

No. 23-2042

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**In the United States Court of Appeals  
for the Federal Circuit**

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JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARMACEUTICA NV,  
AND JANSSEN RESEARCH & DEVELOPMENT, LLC,

*Plaintiffs-Appellees,*

*v.*

MYLAN LABORATORIES LTD.,

*Defendant-Appellant.*

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Appeal from the U.S. District Court for the District of New Jersey  
No. 2:20-cv-13103, Hon. Evelyn Padin

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**NON-CONFIDENTIAL JOINT APPENDIX**

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## TABLE OF CONTENTS

Description	Page
Final Judgment (May 23, 2023) .....	Appx00001
Opinion (May 15, 2023) .....	Appx00004
U.S. Patent No. 10,143,693 B2 (DTX-001) .....	Appx00078
Docket Sheet, <i>Janssen Pharmaceuticals, Inc. v. Mylan Laboratories Ltd.</i> , No. 2: 20-cv-13103 (D.N.J.) .....	Appx00097
Letter from K. Miller, Esq. to Hon. Lois Goodman, <i>Janssen v. Mylan</i> (June 28, 2022) (Docket No. 72) .....	Appx00204
Opening Expert Report of Roger W. Sommi, Jr., Pharm.D. (March 9, 2022) (Exhibit 2 to June 28, 2022 Letter) (Docket No. 72-2) .....	Appx00221
Emails between L. Campbell-Verduyn and L. Soderstrom (April 18, 2022) (Exhibit 7 to June 28, 2022 Letter) (Docket No. 72-7) .....	Appx00368
Mylan's Non-Infringement Contentions (May 26, 2021) (Exhibit A to June 28, 2022 Letter) (Docket No. 72-11) .....	Appx00484
Letter Order, <i>Janssen v. Mylan</i> (August 4, 2022) (Docket No. 78) ..	Appx00719
Plaintiffs' Motion in Limine to Exclude Mylan's Divided Infringement Defense (August 19, 2022) (Docket No. 81) .....	Appx00724
Final Pretrial Order, <i>Janssen v. Mylan</i> (September 22, 2022) (Docket No. 99) .....	Appx00946
Transcript of Oral Argument, <i>Janssen v. Mylan</i> (October 20, 2022) .....	Appx01105
Order, <i>Janssen v. Mylan</i> , (October 20, 2022) (Docket No. 121) .....	Appx01165

Mylan’s Opening Post Trial Brief, <i>Janssen v. Mylan</i> (January 24, 2023) (Docket No. 135) .....	Appx01166
Janssen’s Opening Post Trial Brief, <i>Janssen v. Mylan</i> (January 24, 2023) (Docket No. 137) .....	Appx01260
Trial Transcript, Volume 1, <i>Janssen v. Mylan</i> (November 16, 2022) (Docket No. 158) .....	Appx01863
Trial Transcript, Volume 2, <i>Janssen v. Mylan</i> (November 30, 2022) (Docket No. 160) .....	Appx02054
Trial Transcript, Volume 3, <i>Janssen v. Mylan</i> (December 1, 2022) (Docket No. 161) .....	Appx02352
Trial Transcript, Volume 4, <i>Janssen v. Mylan</i> (December 5, 2022) (Docket No. 162) .....	Appx02584
Trial Transcript, Volume 5, <i>Janssen v. Mylan</i> (December 6, 2022) (Docket No. 164) .....	Appx02768
Trial Transcript, Volume 6, <i>Janssen v. Mylan</i> (December 7, 2022) (Docket No. 166) .....	Appx02930
Trial Transcript, Volume 7, <i>Janssen v. Mylan</i> (December 8, 2022) (Docket No. 168) .....	Appx03125
Trial Transcript, Volume 8, <i>Janssen v. Mylan</i> (December 9, 2022) (Docket No. 170) .....	Appx03289
Notice of Appeal, <i>Janssen v. Mylan</i> (May 26, 2023) (Docket No. 175) .....	Appx03625
Letter from K. Miller to Hon. Z. Quraishi and Hon. L. Goodman, <i>Janssen v. Mylan</i> (September 10, 2021) (Docket No. 40) .....	Appx03691
U.S. Patent No. 10,143,693 (PTX-0001) .....	Appx10000

Invega Trinza Label (May 1, 2015) (PTX-0043) .....	Appx10033
Exhibit 3, Summary of the Patent-in-Suit and Other Patents Related to Invega Trinza or Paliperidone Palmitate (PTX-0089C) .....	Appx10179
ANDA 216228 Proposed Label (June 28, 2021) (PTX-0092) .....	Appx10238
Correll, <i>The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence</i> , J. Clin. Psych 2016:77 (suppl. 3): 1-24 (PTX-0097) .....	Appx10292
Invega Sustenna Prescribing Information (Nov. 1, 2014) (PTX-0106) .....	Appx10331
Berwaerts et al., <i>Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia</i> , JAMA Psychiatry 72(8) (2015): 830 (PTX-0113) ..	Appx10387
U.S. Patent Application Publication No. US 2009/0163519 A1 (PTX-0115) .....	Appx10465
U.S. Patent Application Publication No. US 2011/015536 A1 (PTX-0116) .....	Appx10491
Samtani et al., <i>Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia: A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic</i> , Clin. Pharmacokinet 48(9) (2009): 585-600 (PTX-0118) .....	Appx10511
ANDA 215682 Proposed Label (April 5, 2021) (PTX-0133) .....	Appx10598
ANDA 216228 Proposed Label (June 28, 2021) (PTX-0162) .....	Appx12274
Joshi et al., <i>Baseline Characteristics and Treatment Patterns of Patients with Schizophrenia Initiated On Once-Every-Three- Months Paliperidone Palmitate in a Real-World Setting</i> , Current Med. Research Opinion, 33.10 (2017): 1763-1772 (PTX-0220)....	Appx12873

Paliperidone Palmitate – 546 mg/1.75 mL – Extended-release Injectable Suspension Module 1.14.1.2. Annotated Comparison with Final Labeling (PTX-0595) .....	Appx14094
Application Data Sheet 37 CFR 1.78 for Dosing Regimen for Missed Doses for Long-Acting injectable Paliperidone Esters, Application No. 15090889 (April 5, 2016) (DTX-008) .....	Appx14239
Slides titled “Examining the Pharmacokinetics and Pharmacodynamics of Long-Acting Injectable Antipsychotics, How Best to Individualize Treatment” (DTX-214) .....	Appx17051
Excerpts of Transcript of Deposition of Katie Reed, <i>Janssen v. Mylan</i> (February 2, 2022) .....	Appx22423

## CONFIDENTIAL INFORMATION STATEMENT

The following pages of the district court’s post-trial opinion contain highly confidential information sealed by order of the court: **Appx0009** (nonpublic regulatory information related to Mylan’s proposed PP3M products); **Appx00056** (development of Janssen’s PP3M product); **Appx00065** (financial and sales information related to Janssen’s PP3M product); **Appx00073** (composition of Mylan’s proposed PP3M products). Pages **Appx14094-14112** contain an excerpt of Mylan’s Abbreviated New Drug Application with confidential information sealed by order of the court concerning nonpublic changes to the application.

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS,  
INC., JANSSEN PHARMACEUTICA  
NV, and JANSSEN RESEARCH &  
DEVELOPMENT, LLC,

*Plaintiffs,*

v.

MYLAN LABORATORIES LIMITED,

*Defendant.*

Civil Action No. 2:20-cv-13103-EP-  
LDW

(Consolidated)

**FINAL JUDGMENT**

IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. This Court has jurisdiction over Plaintiffs Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, and Janssen Research & Development, LLC (collectively, “Janssen”); Defendant Mylan Laboratories Limited (“Mylan”)<sup>1</sup>; and the subject matter of this action.

2. For the reasons set forth in the Court’s Opinion dated May 15, 2023 (D.I. 171), and as reflected in the Court’s Order of the same date (D.I. 172), Final

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<sup>1</sup> Pursuant to the Stipulation and Order Dismissing Without Prejudice Defendants Mylan Pharmaceuticals Inc. and Mylan Institutional LLC and Amending Caption in the Action to Reflect the Same (D.I. 5), Mylan Pharmaceuticals Inc. and Mylan Institutional LLC are bound by this Final Judgment, as well as any Judgment, Order, or decision, including any injunction, rendered as to Mylan in this Action.

Judgment is entered in favor of Janssen and against Mylan on all claims and counterclaims with respect to infringement and validity of claims 5-7 and 9-14 of United States Patent No. 10,143,693 (“the ’693 patent”) and Mylan’s products that are the subject of ANDA Nos. 216228, 212290, and 215682.

3. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Mylan’s ANDA Nos. 216228, 212290, and 215682 shall be no earlier than the date of expiration of the ’693 patent (currently April 5, 2036).

4. In accordance with 21 C.F.R. § 314.107(e), Mylan shall submit a copy of this Final Judgment to the FDA within fourteen (14) days of the date of entry of this Final Judgment by the Court.

5. Pursuant to Fed. R. Civ. P. 54, L. Civ. R. 54.1, and 28 U.S.C. § 1920, Janssen may seek its costs, subject to Paragraphs 6 and 7, in an amount to be determined by the Clerk of the Court.

6. In the event that a party appeals this Final Judgment, any motion for attorney fees and/or costs, including any bill of costs or motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after the expiration of the time to petition for certiorari to the United States Supreme Court or, if the appeal is withdrawn or dismissed, within 60 days after such withdrawal or dismissal.

7. In the event that no party appeals this Final Judgment, any motion for

attorney fees and/or costs, including any bill of costs or motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within 60 days after the expiration of the time for filing a notice of appeal under Fed.

R. App. P. 3 and 4.

8. This is a final, appealable judgment.

**IT IS SO ORDERED**, on this 23rd day of May, 2023.



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Hon. Evelyn Padin  
United States District Judge

**NOT FOR PUBLICATION**

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS, INC., *et al.*,

Plaintiffs,

v.

MYLAN LABORATORIES LTD.,

Defendant.

No. 20cv13103 (EP) (LDW)

**OPINION**

**Padin, District Judge.**

<b>I. INTRODUCTION.....</b>	<b>3</b>
<b>II. BACKGROUND .....</b>	<b>5</b>
A. The Hatch-Waxman Act/ANDAs .....	5
B. Parties, jurisdiction, and standing .....	6
C. Background for the invention .....	7
1. Schizophrenia and antipsychotic medications .....	7
2. Medication nonadherence .....	8
3. Pharmacokinetics, Population Pharmacokinetics, and depot formulations .....	9
D. Trinza .....	10
E. The patent at issue: the 693 Patent.....	11
1. Prosecution History.....	11
2. The Patent Specification .....	12
F. The Asserted Claims .....	13
G. Mylan's Proposed Labels .....	15
<b>III. ANALYSIS .....</b>	<b>16</b>
<b>A. INFRINGEMENT: Janssen established that Mylan's Proposed Labels will induce HCPs to infringe upon the Asserted Claims.....</b>	<b>16</b>
1. Mylan's Proposed Labels essentially duplicate Janssen's and recite each limitation of the Asserted Claims .....	17
a. Claim 5 .....	18
b. Claims 6 and 7 .....	21
c. Claim 10.....	21
d. Claims 11 and 14 .....	21
2. Mylan's divided infringement defense .....	22
a. Mylan's divided infringement defense fails because it was untimely .....	24



b. Even if the divided infringement defense had been timely, the Court agrees with Janssen that a single entity (a healthcare provider) performs the claimed reinitiation dosing regimen's three steps .....	25
3. Mylan specifically intended to induce infringement.....	30
a. The explicit instructions in Mylan's Proposed Labels establish specific intent ...	30
4. Allegedly noninfringing uses do not defeat infringement .....	35
<b>B. OBVIOUSNESS: Mylan failed to prove through clear and convincing evidence that the asserted claims of the 693 Patent would have been obvious to a persona of ordinary skill in the art ("POSA") .....</b>	<b>36</b>
1. The PP3M prior art was likely considered by the PTO Examiner.....	37
2. Mylan failed to prove that every element of the Asserted Claims was known in the prior art.....	38
a. The Sustenna label .....	42
b. 4-5 Half-Life extrapolation theory .....	43
c. Dr. Forrest's JAMA "natural jump" theory .....	46
d. Samtani 2009 .....	48
i. Dr. Forrest selectively utilized just a few parameters influencing PK .....	49
ii. Dr. Forrest's model ignored PP1M's complex absorption .....	50
iii. Dr. Forrest extrapolates PP3M's absorption rate (Ka) from PP1M.....	51
iv. Dr. Forrest's "validation".....	52
3. Mylan failed to prove motivation to combine prior art to arrive at the Asserted Claims with a reasonable expectation of success.....	54
a. Mylan did not prove any motivation to treat the 4-9 month missed dose patient population with a reasonable expectation of success.....	54
b. Mylan did not prove any motivation to use, or a reasonable expectation of success in combining the elements of the prior art .....	54
c. Mylan did not prove any motivation to use, or a reasonable expectation of success in using, PP1M to reinitiate PP3M .....	57
4. Objective indicia of the Asserted Claims' nonobviousness .....	58
a. The Asserted Claims' dosing regimens helped Trinza fulfill the long-felt but unmet need for a longer, second-generation LAI .....	59
b. The Asserted Claims' dosing regimens have contributed to Trinza's commercial success.....	61
i. Trinza is a commercial success.....	62
ii. There is a nexus between the Asserted Claims and Trinza's success .....	63
c. Skepticism of the Asserted Claims' efficacy .....	65
<b>C. INVALIDITY: Mylan failed to establish that the Asserted Claims are invalid.....</b>	<b>66</b>
1. The Asserted Claims are enabled.....	66
a. The specification provides enough information to practice the Asserted Claims	67
b. "PP1M" and "PP3M" are not unduly broad .....	68
c. The <i>Wands</i> factors support enablement .....	71
2. The Asserted Claims do not lack written description .....	72
<b>IV. CONCLUSION .....</b>	<b>73</b>

## I. INTRODUCTION

This is a Hatch-Waxman Act case. Plaintiffs Janssen Pharmaceuticals, Inc. (“JPI”), Janssen Pharmaceutica NV (“JPN”), and Janssen Research & Development, LLC (“JRD”), collectively “Janssen,” manufacture Invega Trinza (“Trinza”), an FDA-approved, three-month long-acting injectable paliperidone palmitate (PP3M)<sup>1</sup> for treating schizophrenia and similar conditions. Defendant Mylan Laboratories Limited (“Mylan”) seeks to use the Abbreviated New Drug Application (“ANDA”) process to market a generic version of Trinza. Mylan’s generic and its label are substantively identical to Trinza and Trinza’s label.

But this case is not about the Trinza patent, which has expired. Janssen also has an active patent for a PP3M dosing regimen to reinitiate patients onto PP3M 4 to 9 months after a missed dose using a one-month long-acting injectable paliperidone palmitate (PP1M), then PP3M (the “693 Patent” or the “Patent”). Janssen asserts that Mylan’s generic label, if the generic product comes to market, will inevitably induce health care providers (“HCPs”) to infringe the 693 Patent’s reinitiation regimen. And Mylan seeks to prove the 693 Patent’s invalidity, arguing that the Patent’s reinitiation dosing regimen, under various theories, should not (and/or never should have been) protected by patent law. Mylan’s primary theory was obviousness, *i.e.*, that a person of ordinary skill in the art (“POSA”) could have formulated the 693 Patent’s claims using information publicly available before the Patent’s issuance.

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<sup>1</sup> Paliperidone Palmitate is abbreviated herein as “PP.”

After a bench trial<sup>2</sup> and extensive post-trial briefing,<sup>3</sup> and having weighed the credible testimony and other evidence in the record, the Court finds that: (1) Janssen has demonstrated by a preponderance of the evidence that Mylan will inevitably induce HCPs to infringe the Patent's Asserted Claims (defined below); and (2) Mylan has not demonstrated by clear and convincing evidence that the 693 Patent is obvious or otherwise invalid.<sup>4</sup> The Court will therefore enter judgment against Mylan, and for Janssen, as to the 693 Patent.

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<sup>2</sup> Trial was held on November 16 and 30 and December 1, 5, 6, 7, 8, and 9, 2022, and closing arguments on March 16, 2023. The Court acted as the trier of fact, adopting the standards utilized by a jury to evaluate credibility and weigh evidence. *See* Model Jury Charges of the Third Circuit, §§ 1.5, 1.6, and 1.7. The following witnesses testified for Janssen's infringement case: for Janssen, Roger Sommi, University of Missouri-Kansas City Professor of Pharmacy Practice; and for Mylan, Dr. Steven Berger, Board-Certified forensic and general psychiatrist. Next, for Mylan's primary invalidity case: for Mylan, Dr. Laird Forrest, University of Kansas Professor of Pharmaceutical Chemistry; and for Janssen, Jogarao Gobburu, University of Maryland Professor of Pharmacy Practice and Science; Steven Little, University of Pittsburgh Professor of Pharmaceutical Sciences, Immunology, and Bioengineering; and Dr. Sommi. And finally, regarding secondary considerations: for Mylan, Dr. Jeffery Stec, Berkeley Research Group Managing Director, and Drs. Berger and Forrest; and for Janssen, Dr. Christian Kohler, University of Pennsylvania School of Medicine Clinical Director of Neuropsychiatry; and Carla Mulhern, Managing Principal of Analysis Group.

<sup>3</sup> The Court extends its sincere appreciation to counsel for their professionalism, dedication, and collegiality during litigation and trial.

<sup>4</sup> This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

## II. BACKGROUND

### A. The Hatch-Waxman Act/ANDAs

Under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq., the FDA must approve all new drugs before distribution in interstate commerce. 21 U.S.C. § 355(a). To secure new drug approval, an applicant may file a New Drug Application (“NDA”) that includes the number and expiration date of any patents which claim the drug, or a method of using the drug, if an infringement claim could reasonably be asserted. *Id.* § 355(b)(2). “The FDA publishes the names of approved drugs and their associated patent information in the Approved Drug Products with Therapeutic Equivalence Evaluations list a/k/a the ‘Orange Book.’” *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045 (Fed. Cir. 2010). An applicant seeking approval to market a generic version of an already-approved drug may file an Abbreviated NDA (“ANDA”), which “allows an applicant to rely on the safety and efficacy information for the listed drug if the applicant can show that the generic drug is ‘bioequivalent’ to the listed drug.” *Id.* (citing 21 U.S.C. §§ 355(b)(2), 355(j)).

The Hatch-Waxman Act<sup>5</sup> aims to balance two competing policy interests: research and development of new drugs enabling competitors to bring low-cost generic copies of those drugs to market rapidly if those drugs are not entitled to patent protection. *See Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002). To balance those interests, the Hatch-Waxman Act provides a means for pharmaceutical companies to resolve patent disputes relatively quickly. Ideally, it provides for a prompt determination of whether particular drugs made and sold

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<sup>5</sup> The more common name for the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360(c), 35 U.S.C. §§ 156, 271, 282), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066.

by brand-name pharmaceutical companies are protected by valid patents. If the patents are held to be infringed and not invalid, the covered drugs cannot be made and sold by generic manufacturers until the patents expire. If the patents are held to be invalid or not infringed, the Act provides for prompt approval of the generic versions of the drugs by the FDA, which regulates the sale of pharmaceutical drugs in this country.

The Hatch-Waxman Act creates what is referred to as an “artificial” type of infringement that allows for the adjudication of the parties’ rights in patents that would be infringed if the ANDA were issued and the generic product made, used, or sold. *See Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004). In particular, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of patent infringement to submit an ANDA for a drug claimed in a patent or the use of which is claimed in a patent if the purpose of the ANDA’s submission is to obtain approval to manufacture, use, or sell the patented drug. If a patent infringement suit is commenced within 45 days of a generic manufacturer notifying a brand-name manufacturer of the ANDA application, then the FDA may not approve the ANDA application until the expiration of a 30-month statutory period. *Id.* § 355(c)(3)(C).<sup>6</sup>

**B. Parties, jurisdiction, and standing**

Plaintiffs are JPI, JPN, and JRD (collectively “Janssen”). D.E. 99 (Final Pre-Trial Order (“FPTO”)) 2 n.1, 6-8.<sup>7</sup> JPN owns the entire right, title, and interest in the 693 Patent and JPI holds New Drug Application (“NDA”) No. 207946 for paliperidone palmitate three-month extended release injectable suspension (“PP3M”) prescribed and sold under the Trinza trademark. FPTO 11, 14; PTX-2; PTX-3; PTX-4.

<sup>6</sup> [REDACTED]

<sup>7</sup> Unless otherwise indicated, the Court cites to the FPTO’s Stipulations of Fact contained in Section III. *See* FPTO 2, *et seq.*

Defendant Mylan Laboratories Limited (“Mylan”) is a generic drug manufacturer who has filed Abbreviated New Drug Application (“ANDA”) Nos. 212290, 215682, and 216228, seeking United States Food & Drug Administration (“FDA”) approval to market a generic version of Janssen’s Invega Trinza Product (“Mylan’s Proposed ANDA Products”). FPTO 5, 33, 38, 43.

Because this action arises under United States patent laws, this Court exercises subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a); FPTO 1-2. JPN and JPI have standing to bring this suit. *Schwendimann v. Arkwright Advanced Coating, Inc.*, 959 F.3d 1065, 1072 (Fed. Cir. 2020).

### **C. Background for the invention**

#### *1. Schizophrenia and antipsychotic medications*

Schizophrenia is a serious and disabling mental illness that affects about 1% of the population. Tr. 175:5-6 (Berger), 870:3-17 (Kohler). Schizophrenia is a type of psychosis, *i.e.*, a loss of contact with reality with positive symptoms (delusions, hallucinations) and negative symptoms (alogia, avolition) affecting the ability to manage day-to-day responsibilities, relationships, education, and employment. Tr. 54:9-55:6 (Sommi), 176:1-8 (Berger). Schizophrenia patients are often unemployed, poverty-stricken, homeless, and/or incarcerated. Tr. 58:14-17 (Sommi), 175:9-21 (Berger). The “largest mental health provider for schizophrenics” in the United States is the prison system. Tr. 902:16-19 (Kohler).

Schizophrenia has no cure. Tr. 56:21-22 (Sommi), 176:9-11 (Berger). Instead, practitioners aim for symptom improvement and relapse prevention through antipsychotic medications. Tr. 56:23-57:6, 58:1-13 (Sommi), 176:12-17 (Berger), 871:3-9 (Kohler). First-generation antipsychotics, like Thorazine (chlorpromazine), were introduced in the 1950s. Tr. 177:10-17 (Berger). They worked by targeting dopamine and came in the form of tablets, then

liquids, then short-acting injectables, then long-acting injectables. Tr. 59:16-61:20 (Sommi), 177:10-17 (Berger). Long-acting injectable antipsychotics (“LAIAs”) have been available since at least the 1960s. Tr. 61:16-19 (Sommi).

Second-generation antipsychotics, which targeted serotonin, emerged in the 1980s with clozapine; like their first-generation predecessors, as pills, then liquids, then short-acting and long-acting injections. Tr. 177:18-23 (Berger). Though mitigating some first-generation side effects, the second-generation antipsychotics caused new, metabolic side effects like weight gain, increased risk of diabetes, and increased blood glucose. Tr. 60:23-61:9 (Sommi).

Continuous antipsychotic treatment avoids relapse; with each relapse, schizophrenia progresses to further loss of brain function and becomes harder to treat. Tr. 68:18-69:5 (Sommi), 871:9-21 (Kohler).

## *2. Medication nonadherence*

Nonadherence accompanies the management of all chronic diseases, but is particularly prevalent and well-documented among schizophrenia patients. Tr. 67:4-9 (Sommi) (noting that 75% of patients over 18-month period stopped taking oral antipsychotics), 182:15-17 (Berger), Tr. 932:15-20 (Kohler), 1034:18-20 (Berger); PTX-97 at 15-16. Among the reasons for medication nonadherence are side effects associated with antipsychotics. Tr. 72:10-13 (Sommi), 911:1-3 (Kohler). Accordingly, clinicians seek to avoid those side effects. Tr. 873:1-11.

LAIAs, which reduce the “number of times the patient has to remember to take the medication,” improve nonadherence. Tr. 1034:24-1035:6, (Berger), 873:19-21 (Kohler); Gopal Dep. Tr. 176:20-177:4; PTX-97 at 18. LAIAs enhance patient convenience, reduce relapses (which improves patient prognoses), and reduce caretaker burdens. Tr. 68:13-70:10 (Sommi). Moreover, because HCPs administer LAIAs, they can more accurately track medication adherence

and thereby assess patient response. Tr. 70:11-25 (Sommi). Nevertheless, despite LAIA benefits, HCPs—particularly “younger staff members”—are sometimes reluctant to prescribe them, in part because “many clinicians lack knowledge about practical issues, ... including dose selection, pharmacokinetics, and what to do when a patient is late for an injection or has persistent symptoms after starting therapy.” PTX-97 at 17.

### 3. *Pharmacokinetics, Population Pharmacokinetics, and depot formulations*

Pharmacokinetics is the practice of describing how a given drug will behave in a patient’s body, *i.e.*, “what the body does to a drug” through absorption, distribution, metabolism, and excretion—how it enters, how it’s processed, and how it leaves. Tr. 401:23-402:5 (Forrest), 806:23-807:28 (Gobburu). Monitoring pharmacokinetics requires obtaining drug levels by taking blood samples from patients and measuring drug levels at various points in time. Tr. 807:9-11 (Gobburu). Drug levels are then plotted on a plasma concentration time curve. Tr. 807:11-13 (Gobburu).

Depot drugs are drug formulations that last in a patient’s body for different amounts of time. Tr. 400:22-401:5 (Forrest). An individual’s response to a drug—including a depot drug—is unpredictable due to “genetics, disease, age, gender, body weight, drugs given concomitantly, and various behavioral and environmental factors.” Tr. 807:5-19 (Gobburu); PTX-145<sup>8</sup> at 500. The response may also vary depending upon a drug’s particle size. Tr. 400:25-401:5 (Forrest). Population pharmacokinetics (“pop-PK”), used in designing dosing regimens, accounts for these variations and allows scientists to “understand not only the average ... but the spread of the data.” Tr. 808:21-809:5 (Gobburu). To devise the claimed dosing regimens, the 693 Patent’s inventors

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<sup>8</sup> Rowland, Malcolm and Tozer, Thomas N., *Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications*, Fourth Edition (2011), Wolters Kluwer.



developed a “comprehensive [pop-PK] model” for PP and used that model to simulate various dosing regimen scenarios. PTX-1 at 17:25-46, 19:55-20:28, Figs. 4A-4C.

When a patient receives their first injection of a depot drug they have not previously been administered or are otherwise naïve to, they begin at zero concentration at zero time on a plasma curve. Tr. 402:18-25 (Forrest). For a typical injectable depot drug, a patient’s plasma curve rises “very quickly.” Tr. 403:11-19 (Forrest).

#### **D. Trinza**

Trinza, approved in May 2015, is a three-month long-acting injectable (“LAI”) formulation of the second-generation antipsychotic PP. Tr. 73:22-25, 74:8-11 (Sommi). Invega Sustenna was the one-month, PP1M formulation. Tr. 74:1-3 (Sommi). When Trinza was launched, it was lauded as “revolutionary.” PTX-226<sup>9</sup> at 5. It remains the only LAIA administered once every three months. Tr. 74:23-75:6 (Sommi).

When Trinza launched, HCPs had no experience with a three-month dosing regimen. Tr. 74:23-75:2 (Sommi), 874:22-875:1 (Kohler). HCPs had concerns about effectiveness and side effects; as to the latter, HCPs recognized that any side effects would have to be managed “over a much longer period of time.” Tr. 875:1-24 (Kohler), Tr. 1058:15-16 (Berger) (acknowledging reluctance to prescribe Trinza: “We were questioning whether it would really last three months”).

Trinza has been “very well received,” has “fulfilled [HCP] expectations in providing effective treatment over a period of at least three months in people who were previously stabilized ... [on] Invega Sustenna,” and has demonstrated a “tolerable side effects profile.” Tr. 876:2-9 (Kohler). Even Mylan’s expert, Dr. Berger, hails it as a “wonderful drug.” Tr. 243:23-24.

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<sup>9</sup> Daghistani & Rey, *Invega Trinza: The First Four-Times-a-Year, Long-Acting Injectable Antipsychotic Agent*, P&T, Vol. 41, No. 4 (Apr. 2016).

**E. The patent at issue: the 693 Patent**

The 693 Patent “relates to a method for treating patients who have missed a treatment of 3-month paliperidone palmitate extended-release injectable suspension formulation.” PTX-1 at 1:15-19, 17:16; Tr. 76:17-76:18 (Sommi). The Asserted Claims describe dosing regimens for administering PP to a patient that had been last administered PP3M 4 to 9 months ago. *See* PTX-1 at Claim 5.

*1. Prosecution History*

On April 5, 2016, Janssen filed the application that became the 693 Patent. FPTO 13. The application included Claims 1-8. DTX-8 at 40-42.

On November 1, 2017, the Patent Office Examiner (“Examiner”) conducted prior art searches on the East and Google Scholar Databases. DTX-8 at 193. The Examiner’s East search queries included “paliperidone,” “three month,” and the inventor names; the Examiner’s Google Scholar search terms are not recorded. DTX-8 at 205-06.

On November 20, 2017, the Examiner rejected claims 1-8 as obvious over the 536 Publication in view of certain prior art, Osborne,<sup>10</sup> and on the ground of nonstatutory obviousness-type “double patenting” over claims 1-16 of U.S. Patent No. 9,439,906 (the “906 Patent”), which covers PP1M initiating (not re-initiation) dosing regimens. DTX-8 at 196-203. The Examiner did not reject the claims under 35 U.S.C. § 112, *i.e.*, lack of specification. *Id.*; Tr. 768:1-11 (Forrest).

In response to the double patenting rejection, Janssen argued that the 906 Patent concerned *PP1M’s initial* dosing regimen, not the subject claims relating to a *missed PP3M* dosing regimen.

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<sup>10</sup> Osborne et al., *Health-related quality of life advantage of long-acting injectable antipsychotic treatment for schizophrenia: a time trade-off study*, *Health and Quality of Life Outcomes* 10(35) (2012): 1-9; DTX-36.

DTX-8 at 217. In other words, a *missed PP3M* dosing regimen would not double-patent an *initial PP1M* dosing regimen. *Id.*

On June 14, 2018, the Examiner conducted updated searches on East and Google Scholar. *Id.* 236. Again, the East searches included “paliperidone,” “three month,” and the inventors’ names. *Id.* 237. On June 27, 2018, the United States Patent and Trademark Office (“PTO”) issued a Notice of Allowance, concluding that the 693 Patent’s rejected claims are patentable. DTX-8 at 223. The PTO reasoned:

While the closest prior art of 536 publication teaches a dosing regimen for a patient to get back onto PP1M after missed dose of PP1M, the prior art does not teach [PP3M] and exact numbers of reinitiation loading doses and maintenance doses and their amounts for patients who had been treated with a PP3M and had been last administered the PP3M more than 9 months or 4 to 9 months ago as claimed. No other prior art was found to teach that when a patient misses a dose of PP3M for extended period of time a patient must first be treated and stable on PP1M and then a PP3M injection is then given at the time that the patient would have received their next PP1M injection as claimed. Thus, the instant claims are novel and non-obvious over the prior art.

*Id.* 229.

The 693 Patent issued on December 4, 2018.

## 2. *The Patent Specification*

The 693 Patent’s specification explains that PP3M “offers the prospect of fewer opportunities for nonadherence than currently available [LAI] formulations, thus reducing relapse risk as a result of subtherapeutic plasma concentration and its associated negative consequences in patients with schizophrenia.” PTX-1 at 2:15-19. In other words, PP3M works because there are fewer chances for the drug to wear off because of a missed dose.

But missed doses still happen. *Id.* 2:20-22. “Consequently, there is a need to reinitiate a dosing regimen for patients who miss their regularly scheduled dose of medication.” *Id.* 2:22-24.

“Thus, the objective of the present application is to provide a dosing regimen of [PP] for patients in need of a treatment who have missed their 3 month ( $\pm 2$  weeks) dose of [PP3M].” *Id.* 2:24-29.

The specification summarizes the claimed dosing regimens. *Id.* 2:32-3:56. It describes a “dosing regimen for administering an injectable [PP] depot to a patient in need of psychiatric treatment that has been treated with” PP3M, “wherein said patient misses for a period of between about four months and about nine months” the “next scheduled maintenance dose” of PP3M. *Id.* 2:32-42. The claimed dosing regimens “compris[e]” three numbered doses of PP1M or PP3M corresponding to the Asserted Claims.

The specification also provides detailed information about PP1M and PP3M formulations for use in the dosing regimens, including:

- Composition for the 1-month and 3-month formulations: the active ingredient (PP), the types of inactive ingredients, the concentrations of the ingredients. PTX-1 at 13:49-56, 13:62-14:3.
- Average and preferred particle size ranges for PP1M and PP3M. *Id.* 9:39-51.
- PP1M and PP3M manufacturing instructions. *Id.* 11:23-29, 11:50-12:35.
- Examples of PP1M and PP3M formulations that disclose specific inactive ingredients. *Id.* 4:33-39, 13:56-62.
- Description of Sustenna and Trinza as commercial embodiments of PP1M and PP3M, respectively. *Id.* 4:18-20, 5:23-25, 5:44-46, 6:63-65.

#### **F. The Asserted Claims**

The 693 Patent’s Asserted Claims include independent claim 5 and dependent claims 6-7 and 9-14. All dependent claims depend directly or indirectly from claim 5. *See* PTX-1 at 21:10-22:3. As goes claim 5, so go the rest.

Claim 5 claims a PP3M reinitiation dosing regimen for a patient who had their last dose 4 to 9 months prior:

A dosing regimen for administering an injectable paliperidone depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with PP3M, wherein said patient had been last administered a PP3M

injection 4 to 9 months ago and the next scheduled maintenance dose of PP3M should be administered to said patient, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M;
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4<sup>th</sup> day to about the 12<sup>th</sup> day after administering of said first reinitiation loading dose; and
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day after administering the second reinitiation loading dose of PP1M wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose

Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M
175 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	525 mg eq.

Claims 6-7 depend directly from claim 5 and narrow this method to a specific patient in need of treatment for psychosis (claim 6) and schizophrenia (claim 7). *Id.* 21:40-43.

Claim 9 depends directly from claim 5 and narrows this method to a specific time for administering the second PP1M reinitiation dose to “about 7 days” after the first PP1M reinitiation loading dose. *Id.* 24:49-51.

Claim 11 depends directly from claim 5 and narrows this method to a specific time for the administering of the PP3M reinitiation dose to “about 30 days” after the second PP1M reinitiation loading dose. *Id.* 21:52-54. Claim 12 depends from claim 11 and narrows this method to a specific time for administering the PP3M reinitiation dose to “30 days” after the second PP1M reinitiation loading dose. *Id.* 21:55-57.

Claim 13 depends directly from claim 5 and narrows this method to a specific time for administering the PP3M reinitiation dose to “about a month” after the second PP1M reinitiation loading dose. *Id.* 21:58-60. Claim 14 depends from claim 11 and narrows the method to a specific time for administering the PP3M reinitiation dose to “a month” after the second PP1M reinitiation loading dose. *Id.* 22:1-3.

The 693 Patent covers Trinza. FPTO 4. In turn, Trinza’s label dosing instructions track the 693 Patent’s Asserted Claims. Specifically, Trinza’s label instructs HCPs not to administer the next Trinza dose if a patient missed a dose between 4 and 9 months prior, but to use the reinitiation regimen shown in the table above. PTX-43 at 5. That table tracks the Asserted Claims. Tr. 88:14-92:8 (Sommi), Tr. 244:14 (Berger).

#### **G. Mylan’s Proposed Labels**

Mylan filed ANDA Nos. 216228, 212290, and 215682 seeking FDA approval to market and sell Mylan’s Proposed ANDA Products in 273, 410, 546, and 819 mg PP dose strengths. FPTO 33, 38, 43. The proposed labels (“Mylan’s Proposed Labels”) are substantially identical to the Trinza label. PTX-92 (216228); PTX-162 (212290); PTX-133 (215682). Other than replacing the Trinza and Sustenna brand names with generic names, the Proposed ANDA Products include the same text in the “Missed Doses” section. FPTO 25.

Mylan’s Proposed Labels state: “To manage missed doses on exceptional occasions, refer to the Full Prescribing Information. (2.3).” PTX-92, PTX-133, PTX -162 at 1; PTX-595 at 5. Section 2 of Mylan’s Proposed Labels is entitled “Dosage and Administration.” PTX-92, PTX-133, PTX-162 at 4; PTX-595 at 9. And Section 2.3 is entitled “Missed Doses.” PTX-92, PTX-133, PTX-162 at 6; PTX-595 at 14. Table 2 of the Proposed Labels’ missed dosing regimen reproduces (except for the Sustenna name) Claim 5’s PP3M reinitiation regimen using PP1M:

**Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of Paliperidone Palmitate Extended-Release Injectable Suspension**

If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension was:	Administer 1-month paliperidone palmitate extended-release injectable suspension, two doses one week apart (into deltoid muscle)		Then administer 3-month paliperidone palmitate extended-release injectable suspension (into deltoid <sup>a</sup> or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

<sup>a</sup> See Instructions for Use for deltoid injection needle selection based on body weight.

PTX-92, PTX-133, PTX-162 at 7; PTX-595 at 15. On November 15, 2022, Mylan produced to Janssen an updated proposed label that Mylan had submitted to the FDA. PTX-595; Tr. 103:19-21.<sup>11</sup>

### III. ANALYSIS

#### A. INFRINGEMENT: Janssen established that Mylan's Proposed Labels will induce HCPs to infringe upon the Asserted Claims

It is “an act of [patent] infringement to submit” an ANDA “for a drug claimed in a patent or the use of which is claimed in a patent.” 35 U.S.C. § 271(e)(2); *see Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990). In ANDA cases, the infringement analysis “is focused on a comparison of the asserted patent [claims] against the product that is likely to be sold following ANDA approval.” *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1125 (Fed. Cir. 2018) (cleaned up).

Janssen contends that Mylan, a generic manufacturer, will induce infringement of the Asserted Claims rather than directly practice them. “Whoever actively induces infringement of a patent shall be liable as an infringer.” 35 U.S.C. § 271(b). To establish induced infringement, a plaintiff must prove (1) direct infringement and (2) that the defendant had the specific intent to

<sup>11</sup> Any changes to Mylan's Proposed Labels did not impact the infringement analysis.



induce infringement. *Vanda*, 887 F.3d at 1129. A patentee must prove infringement by a preponderance of the evidence. *Id.* at 1125.

For the reasons detailed below, Janssen has demonstrated by a preponderance of the evidence that Mylan will induce infringement of the Asserted Claims. Specifically, Janssen presented evidence that: (1) Mylan’s Proposed Labels expressly instruct HCPs to infringe the Asserted Claims for patients who last received PP3M 4 to 9 months ago for reinitiation onto PP3M; (2) some patients will inevitably be reinitiated on PP3M between 4 and 9 months after their last dose; and (3) this will inevitably lead some HCPs to practice the patented dosing regimens of the Asserted Claims.

Conversely, the Court is unpersuaded by Mylan’s counterargument—that there is no infringement under a “divided infringement” theory and that many patients will not be treated according to the Asserted Claims. Mylan contends, in substance, that Mylan cannot induce direct infringement because the steps of the claimed dosing regimens will be carried out by two independent actors, neither of which is Mylan: the patient, who missed a dose of PP3M and chose to return for treatment three times, and that patient’s HCP, who would administer the claimed dosing regimen. Tr. 172:24-173:7 (Berger). For the reasons below, this theory lacks any legal or factual basis.

*1. Mylan’s Proposed Labels essentially duplicate Janssen’s and recite each limitation of the Asserted Claims*

In deciding induced infringement, “courts compare[] the wording of the label to the patent claims.” *BTG Int’l Ltd. v. Amneal Pharms. LLC*, 352 F. Supp. 3d 352, 394 (D.N.J. 2018), *appeal dismissed in relevant part as moot*, 923 F.3d 1063, 1077 (Fed. Cir. 2019). Proposed drug labels “encompass infringement” if the “label meets the claim limitations of the patent” or the “label language aligns with the language” of patent claims. *Id.* at 394-95; *see also GlaxoSmithKline LLC*



*v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1330 (Fed. Cir. 2021) (affirming induced infringement where expert “marched through [the] label explaining how it met the limitations of [the] claim”), *reh’g and reh’g en banc denied*, 25 F.4th 949 (Fed. Cir. 2022), *petition for cert. pending*, No. 22-37 (filed July 11, 2022). Here, Dr. Sommi credibly demonstrated that the missed dose instructions in Mylan’s Proposed Labels induce infringement of each element of the Asserted Claims.

a. Claim 5

Claim 5 claims a dosing regimen. PTX-1 at 21:10-11 (“A dosing regimen for administering an injectable [PP] depot ... .”); Tr. 79:25-80:3, 97:17-21, 116:1-2 (Sommi); Tr. 285:7-9 (Berger). Mylan’s Proposed Labels likewise set forth a “reinitiation” dosing regimen. PTX-92 at 4, 6-7 (“2 DOSAGE AND ADMINISTRATION”; “2.3 Missed Doses . . . Table 2. Re-initiation Regimen . . . .”); PTX-133 at 4, 6-7; PTX-162 at 4, 6-7; PTX-595 at 9, 14-15; Tr. 97:17-25 (Sommi).

Next, Claim 5 also identifies a patient in need of treatment for psychosis, schizophrenia, or bipolar disorder. PTX-1 at 21:11-12; Tr. 78:10-12, 97:19-98:3 (Sommi). Mylan’s Proposed Labels also identify a patient in need of treatment for schizophrenia. PTX-92 at 4; PTX-133 at 4; PTX-162 at 4; PTX-595 at 9; Tr. 97:19-98:3 (Sommi).

Claim 5 also identifies a patient who has been treated with PP3M and had been last administered PP3M four to nine months ago. PTX-1 at 21:11-14 (“to a patient ... that has been treated with PP3M, wherein said patient had been last administered a PP3M injection 4 to 9 months ago and the next scheduled maintenance dose of PP3M should be administered to said patient”); Tr. 78:10-12, 82:2-8, 125:19-22 (Sommi), 240:25-241:3 (Berger). Again, Mylan’s Proposed Labels also identify a patient treated with PP3M last administered a dose of PP3M four to nine months ago. PTX-92 at 6-7; PTX-133 at 6-7; PTX-162 at 6-7; PTX-595 at 14-15; Tr. 97:25-98:3, 106:2-15 (Sommi).

Next, Claim 5 identifies the first step of the claimed dosing regimen as “(1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M.” PTX-1 at 21:17-18; Tr. 98:4-6, 123:9-12 (Sommi). And Mylan’s Proposed Labels likewise identify the first reinitiation regimen step as “[a]dminister[ing] 1-month [PP] extended-release injectable suspension . . . (into deltoid muscle) [on] Day 1 [of the re-initiation regimen].” PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:4-8 (Sommi).

Next, Claim 5 identifies the second step of the claimed dosing regimen as “(2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose.” PTX-1 at 21:19-22; Tr. 98:6-9 (Sommi). Mylan’s Proposed Labels likewise identify the second reinitiation regimen step as “[a]dminister[ing] 1-month [PP] extended-release injectable suspension . . . (into deltoid muscle) [on] Day 8 [of the reinitiation regimen]” or seven days after the first reinitiation loading dose of 1-month PP extended-release injectable suspension. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:6-9 (Sommi).

Likewise for the third reinitiation regimen step, which Claim 5 identifies as “(3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M.” PTX-1 at 21:23-26; Tr. 98:10-13, 124:21-23 (Sommi). Mylan’s Proposed Labels also identify the third dosing regimen step as “administer[ing] 3-month [PP] extended release injectable suspension (into deltoid or gluteal muscle) [on] “1 month after Day 8 [of the dosing regimen]” or “1 month” after the second reinitiation dose of PP1M. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:10-13 (Sommi).

Claim 5's table lists the PP1M and PP3M reinitiation dose amounts:

Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M
175 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	525 mg eq.

PTX-1 at 21:31-39; Tr. 98:14-17, 127:3-22 (Sommi). The reinitiation dose amounts are based on the amount of the missed dose of PP3M. PTX-1 at 21:27-29 ("wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose"); Tr. 78:24-79:4 (Sommi). Table 2 of Mylan's Proposed Labels does the same:

**Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of Paliperidone Palmitate Extended-Release Injectable Suspension**

If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension was:	Administer 1-month paliperidone palmitate extended-release injectable suspension, two doses one week apart (into deltoid muscle)		Then administer 3-month paliperidone palmitate extended-release injectable suspension (into deltoid <sup>a</sup> or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

<sup>a</sup> See Instructions for Use for deltoid injection needle selection based on body weight.

PTX-92 at 7; PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:14-17 (Sommi). The dose amounts of the reinitiation doses are similarly based on the amount of the last dose of PP3M and track the amounts in claim 5. PTX-92 at 7; PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:14-17 (Sommi) ("[Y]ou can see that the milligram equivalents in the Claim 5 are exactly the same as the milligrams of the PP1M and PP3M products.").

b. Claims 6 and 7

Claim 6 is “[t]he method of claim 5, wherein said patient is in need of treatment for psychosis.” PTX-1 at 21:40-41; Tr. 100:13-25 (Sommi). Patients with schizophrenia have psychosis and will therefore be in need of treatment for psychosis. Tr. 100:18-25 (Sommi), 176:8 (Berger) (“Schizophrenia is a type of psychosis.”). Accordingly, Mylan’s Proposed Labels also identify a patient in need of treatment for psychosis. PTX-92 at 4; PTX-133 at 4; PTX-162 at 4; Tr. 97:17-98:3, 100:18-101:6 (Sommi).

Similarly, Claim 7 is “[t]he method of claim 5, wherein said patient is in need of treatment for schizophrenia.” PTX-1 at 21:42-43; Tr. 100:16-101:6 (Sommi). Mylan’s Proposed Labels also identify a patient in need of treatment for schizophrenia. PTX-92 at 4; PTX-133 at 4; PTX-162 at 4; Tr. 97:17-98:3, 100:18-101:6 (Sommi).

c. Claim 10

Claim 10 is “[t]he method of claim 9, wherein the second reinitiation dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.” PTX-1 at 21:49-51. Claim 10 specifies that the second step of the claimed dosing regimen is seven days after the first reinitiation loading dose. Tr. 101:7-14 (Sommi). Mylan’s Proposed Labels identify the second administering step of the re-initiation dosing regimen as “[a]dminister[ing] [PP1M] . . . (into deltoid muscle) [on] Day 8 [of the re-initiation regimen],” or seven days after Day 1’s first PP1M reinitiation loading dose. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 101:10-23 (Sommi).

d. Claims 11 and 14

Claim 11 is “[t]he method of claim 5, wherein the reinitiation dose of PP3M is administered about 30 days after administering said second reinitiation loading dose of PP1M.” PTX-1 at 21:52-

54. Claim 11 specifies that the claimed dosing regimen’s third step is about 30 days after the second PP1M reinitiation loading dose. Tr. 102:3-13 (Sommi). Mylan’s Proposed Labels also identify the third administering step of the reinitiation dosing regimen as “administer[ing] [PP3M (into deltoid or gluteal muscle)]” on “1 month after Day 8 [of the re-initiation dosing regimen]” or “1 month” after the second PP1M re-initiation dose on Day 8. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:10-13, 101:24-102:22 (Sommi).

And finally, Claim 14 specifies that the third step of the claimed dosing regimen is about a month after the second PP1M reinitiation loading dose: “[t]he method of claim 11[,] wherein the reinitiation dose of PP3M is administered a month after administering said second [PP1M] reinitiation loading dose.” PTX-1 at 22:1-3; Tr. 102:4-13 (Sommi). As with the other claims, Mylan’s Proposed Labels also identify the third administering step of the reinitiation dosing regimen as “administer[ing] [PP3M] (into deltoid or gluteal muscle) [on] “1 month after Day 8 [of the re-initiation dosing regimen]” or “1 month” after the second PP1M re-initiation dose. PTX-92 at 7 (Table 2); PTX-133 at 7; PTX-162 at 7; PTX-595 at 15; Tr. 98:10-13, 101:24-102:22 (Sommi).

## *2. Mylan’s divided infringement defense*

Janssen alleges, in substance, that Mylan’s proposed Trinza generic will inevitably induce HCPs—those administering the drug to patients—to infringe upon the claimed dosing regimens. Inherent in Hatch-Waxman/ANDA litigation is an element of copying; generic drug manufacturers will often simply stipulate to infringement. 21 U.S.C. § 355(j); *Novartis Pharm. Corp. v. Teva Pharm. USA, Inc.*, No. 05-CV-1887 (DMC), 2009 U.S. Dist. LEXIS 103104, at \*56 (D.N.J. Nov. 5, 2009). This makes logical sense; the FDA requires a generic to be bioequivalent (chemically the same) as the patented substance, with an identical label. Tr. 222:6-20 (Berger).

Here, Mylan contends that there will be no *direct* infringement because the Asserted Claims' reinitiation dosing regimen will be carried out by two independent actors: the patient, who missed a dose of PP3M and chose to return for treatment three times, and that patient's HCP, who administers the claimed dosing regimen. Tr. 172:24-173:7 (Berger). This is the "divided infringement issue." Tr. 204:7-10 (Berger).

Mylan's divided infringement theory posits "seven steps" split between the patient and the HCP:

41. Accordingly, the steps of the claimed method include four (4) steps where the patient is independently responsible and three (3) steps where the healthcare professional is responsible. Accordingly, the steps and party responsible for practicing the steps are as follows:

1. miss a dose (patient);
2. return for treatment between 4 to 9 months since last injection (patient);
3. administering intramuscularly first reinitiation dose of PP1M<sup>30</sup> (healthcare professional);
4. return for treatment on about the 4<sup>th</sup> day to about the 12<sup>th</sup> day after first reinitiation loading dose (patient);
5. administering intramuscularly a second reinitiation loading dose of PP1M (healthcare professional);
6. return for treatment on about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day after second reinitiation loading dose of PP1M (patient); and
7. administering intramuscularly a reinitiation dose of PP3M (healthcare professional).

FPTO, Mylan Contested Facts ¶ 41; Tr. 186:10-188:19; 287:15-20 (Berger).

In contrast, Janssen's infringement theory asserts that the Asserted Claims comprise three steps of administering the three reinitiation doses, numbered as "(1)," "(2)," and "(3)" in the claims. Tr. 79:5-86:25 (Sommi).

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M;
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose; and
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose

a. Mylan's divided infringement defense fails because it was untimely

Local Patent Rule 3.6 sets forth disclosure requirements for Hatch-Waxman Act/ANDA matters, including the disclosure of "Non-Infringement Contentions and Responses" from a "party opposing an assertion of patent infringement." L. Pat. R. 3.2A, 3.6(g). "Local Patent Rules exist to further the goal of full and timely discovery and provide all parties with adequate notice and information with which to litigate their cases," as well as to "require parties to crystallize their theories of the case early in the litigation and to adhere to those theories once they have been disclosed." *Celgene Corp. v. Hetero Labs Ltd.*, No. 17-3387, 2021 U.S. Dist. LEXIS 159262, at \*12 (D.N.J. Mar. 29, 2021) (cleaned up).

Here, Mylan's divided infringement theory was not disclosed in its contentions, and appeared improperly for the first time in Mylan's rebuttal expert report. *See, e.g., Chiesi United States v. Aurobindo Pharma United States*, No. 19-18756, 2022 U.S. Dist. LEXIS 20102, at \*15-16 (D.N.J. Jan. 9, 2022) (granting motion in limine precluding testimony on indefiniteness theory that was not disclosed in contentions); *Celgene*, 2021 U.S. Dist. LEXIS 159262, at \*59 (D.N.J. Mar. 29, 2021) (striking invalidity theory not raised in contentions because it is "impermissible" to introduce new theories in an expert report without amendment); *Merck Sharp & Dohme Corp. v. Sandoz, Inc.*, No. 12-3289 (PGS)(LHG), 2014 U.S. Dist. LEXIS 37002, at \*23 (D.N.J. Jan. 6, 2014) (striking portions of expert reports that rely on prior art not disclosed in contentions).

Janssen argued in pre-trial motions that Mylan did not raise this defense, to Janssen's detriment, until too late in the litigation. Indeed, Mylan's May 26, 2021 Non-Infringement Contentions, presented two theories, neither of which alleged divided infringement. First, Mylan asserted that its Proposed Labels would not directly infringe the reinitiation dosing regimen because Mylan itself does not administer the claimed dosing regimen to the patient; and second,



that Mylan would not have any control over whether patients are treated with the dosing regimen. D.E. 81-3.

Neither of these theories plausibly assert the “seven steps” divided infringement theory that Mylan actually pursued at trial, despite Mylan’s best efforts—*in limine* and now after trial—to shoehorn the theory into its Non-Infringement Contentions. The contentions do not contain the words “divided infringement,” cite no case law on divided infringement, and do not assert that the Asserted Claims have seven steps. *See id.* Rather, the contentions alleged that “*Mylan* will not directly or indirectly infringe the Asserted Claims” because “*Mylan* does not perform the requisite administering step. ... *Mylan* does not cause, urge, encourage, aid, advise, or otherwise induce any particular party to practice any particular claim step that *Mylan*, itself, does not practice, *i.e.*, treating a subject having a disorder.” *Id.* at 4 (emphases added).

Mylan, in other words, was arguing that *Mylan* did not infringe or induce infringement, not—as at trial—that *patients* acted in concert with HCPs to infringe. Even the most expansive reading of Mylan’s Non-Infringement Contentions would not reveal any divided infringement defense. Mylan never sought to amend its Non-Infringement Contentions to add a divided infringement defense; the first mention appeared in Dr. Berger’s expert report. *See* D.E. 72-12. It was therefore untimely. Nevertheless, for the reasons below, it is also unpersuasive on its merits.

- b. Even if the divided infringement defense had been timely, the Court agrees with Janssen that a single entity (a healthcare provider) performs the claimed reinitiation dosing regimen’s three steps

The parties dispute whether a patient’s role constitutes a “descriptor of the clinical situation” (Janssen) or a claimed step (Mylan). As detailed below, the Asserted Claims’ plain language favors Janssen’s interpretation. The Asserted Claims steps are carried out by a single actor: an HCP.



The heart of the infringement dispute here is whether Mylan's Proposed Labels will induce *direct* infringement. Whether the infringement is direct depends on whether any claimed dosing regimen steps will be performed by a second actor—like, according to Mylan, the patient missing a dose and returning for treatment three times. If the HCP is the only actor, Mylan's Proposed Labels will induce infringement by the HCP. If the HCP and the patient are dual actors each performing different claimed steps, there will not be infringement.

Direct infringement “occurs where all steps of a claimed method are performed by or attributable to a single entity.” *Akamai Techs., Inc. v. Limelight Networks*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (*en banc*). “Divided infringement” refers to the situation where “no single actor performs all steps of a method claim.” *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017). When the steps of the method are divided among multiple actors, the claimed method is infringed only if “the acts of one are attributable to the other such that a single entity is responsible for the infringement.” *Id.*

Method-of-treatment claims sometimes have requirements that are not themselves steps of a claimed method. *See, e.g., Pernix Ireland Pain DAC v. Alvogen Malta Operations Ltd.*, 323 F. Supp. 3d 566, 576 (D. Del. 2018) (“mild or moderate hepatic impairment” not a claimed step), *aff'd sub nom., Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184 (Fed. Cir. 2019); *see also* Tr. 28:12-22, 33:9-17 (Mylan's counsel acknowledges that “passive” diagnoses like cancer or schizophrenia are not claimed steps).

The infringement analysis here turns on whether a patient's missed dose or choice to return for the claimed reinitiation regimen are “steps” of the Asserted Claims. Janssen limits its interpretation to the plain language of the Asserted Claims: three reinitiation injections by the HCP, three steps by one actor. Mylan interprets additional steps: the patient missing a dose and returning

three times for the injections (four steps), plus the injections (three more steps, for a total of seven). The Court agrees with Janssen: the injections comprise the only three claimed steps, and an HCP administers each step. Accordingly, Mylan's Proposed Labels will induce direct infringement by a single actor.

Determining the number of steps in a claimed method is a question of "claim construction." *In re Biogen '755 Patent Litig.*, No. 10cv2734, 2016 U.S. Dist. LEXIS 42608, at \*7 (D.N.J. Mar. 28, 2016). "A claim construction analysis must begin and remain centered on the claim language itself." *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "When claim language has as plain a meaning on an issue, ... leaving no genuine uncertainties on interpretive questions relevant to the case, it is particularly difficult to conclude that the specification reasonably supports a different meaning." *Straight Path IP Grp., Inc. v. Sipnet EU S.R.O.*, 806 F.3d 1356, 1360 (Fed. Cir. 2015).

The Asserted Claims "compris[e]" three steps: "administering" the three "reinitiation" doses that are enumerated (1), (2), and (3) in claim 5 to a schizophrenia patient had had their last injection four to nine months prior. PTX-1 at 21:17-29 ("(1) administering . . . ; (2) administering . . . ; (3) administering . . . ."); Tr. 79:5-80:3; 98:4-17, 115:25-116:2, 125:19-22 (Sommi). The dispute centers on the significance of the requirement that a schizophrenia patient miss a dose and return for another four to nine months after the missed dose. Janssen calls this a "descriptor of the clinical situation" in which the claimed dosing regimens are to be administered—not a claimed step. Tr. 82:1-8 ("It just helps me understand who the patient is that I'm treating."), 85:10-18, 86:13-18 ("These are instructions for the [HCP]. These are not instructions to patients. ... These are not drugs that are administered by anybody other than a[n HCP]."), 125:19-22 (Sommi).

But the meaning here is plain: patients arriving *having missed* a dose, and HCPs *administer* three reinitiation doses. The three administrations are the three claimed steps. *See Core Wireless Licensing S.A.R.L. v. Apple Inc.*, No. 15-cv-05008, 2016 U.S. Dist. LEXIS 150795, at \*14 (N.D. Cal. Oct. 31, 2016) (distinguishing the claimed steps, which “each start on a separate line with a gerund . . . demonstrating how the method should be performed,” *e.g.*, storing, inserting, and sending, from other claim limitations, which “describe the environment in which the method . . . is practiced,” *e.g.*, “the radio network controller configured to select”); *Amag Pharm., Inc. v. Sandoz, Inc.*, No. 16-cv-1508, 2017 U.S. Dist. LEXIS 112172, at \*71 (D.N.J. July 19, 2017) (“It is important to remember that the elements, or the body, of a method claim are method steps, which should usually be verbal (gerundial) phrase, introduced by a gerund or verbal noun (the ‘-ing’ form of a verb).”).

It is true, as Mylan argues, that “doses do not miss themselves.” Mylan Resp. Br. 7. But that does not mean, however, that missing a dose is a claimed step. Although having “been last administered a PP3M injection 4 to 9 months ago” is a requirement of the Asserted Claims, it is not a step of the claimed dosing regimens. *See, e.g., Orexigen Therapeutics, Inc. v. Actavis Lab ’ys, FL, Inc.*, 282 F. Supp. 3d 793, 798 (D. Del. 2017) (holding that the act of diagnosing obesity is not a step of a claimed method of treating obesity “comprising administering [a pair of compounds] to an individual who has been diagnosed as suffering from overweight or obesity”);<sup>12</sup> *In re Biogen ‘755 Patent*, 2016 U.S. Dist. LEXIS 42608, at \*4-8 (“produced by” and “transformed by” were

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<sup>12</sup> *Orexigen* rejected a mirror image of Mylan’s divided infringement argument: that the doctor’s initial diagnosis of a patient’s obesity was the first claimed step before the patient administered the drug. But a “plain reading of this claim limitation indicates that the individual will already be diagnosed prior to the method being performed.” *Orexigen*, 282 F. Supp. 3d at 812. In other words, the claimed treatment’s prerequisite (*Orexigen*’s obesity diagnosis and a missed treatment here) has already occurred.

not steps of claimed method because they conveyed action that “‘must have been’ done rather than what ‘must be’ done). Mylan’s contention that a patient’s missed dose or choice to return for treatment can be (or are here) claimed steps lacks any precedential or factual support. To the contrary, there is ample reason to conclude that missing a dose and returning are merely preconditions to administration.

The Asserted Claims’ plain language supports this interpretation in a different way. The dosing regimen is administered “to a patient” who meets certain criteria, including having “been last administered a PP3M injection 4 to 9 months ago.” PTX-1 at 21:10-16; Tr. 84:22-85:2 (Sommi). The use of past-tense language makes clear that the patient missed a dose and returned for treatment *before* the claimed dosing regimens are administered. PTX-1 at 21:13-15 (“wherein said patient had been last administered a PP3M injection 4 to 9 months ago”).

Moreover, the Court cannot agree with Dr. Berger that the tenses used in the Asserted Claims were “irrelevant.” Tr. 286:13-17 (Berger). Elsewhere, he asserted that the passage stating, “wherein said patient had last been administered PP3M four to nine months ago” was the “present tense.” Tr. 286:20-24 (Berger). On cross-examination, however, Dr. Berger conceded that the claim language recites only three steps “in writing,” but stated that the claim language “is not correct” because there are actually “seven steps.” Tr. 290:1-2, 287:19-20, 297:2-11 (“[F]or any treatment that[ i]s administered by a health care professional at a health care facility,” patients “have to show up.”). Dr. Berger took this example to its logical extreme; asked about medications for overdose treatment, he would consider “the patient overdosing to be the first step in a dosing regimen for a drug indicated to treat overdose[.]” Tr. 297:12-19. Or in a baking context, the step preceding mixing eggs with milk would require getting a bowl from the cupboard. Tr. 300:13-19. The theoretical *other* steps might be infinite.

Nor can the Court agree, as Mylan urges, that the Asserted Claims’ prosecution history supports Mylan’s divided infringement theory. Mylan points specifically to Janssen’s statement in the prosecution history that the Asserted Claims “are solely directed to what patients should do if a dose of PP3M is missed and they desire getting back on the medication.” DTX-8 at 217, 0216; *see also* Mylan Resp. Br. 11. This describes what patients should do in the situation where the patient has missed a dose of PP3M—how they arrive at the point where claimed steps (the HCP’s administration) begin, not any active role that patients play in the administration.

Whatever steps Mylan attempts to inject into the Asserted Claims, there are only three claimed “*administering*” steps, and therefore only one administering actor: the HCP. Tr. 96:23-97:7, 139:3-7, 146:10-15 (Sommi); Tr. 291:5-8 (Berger); PTX-92 at 4 (§2.1: “[e]ach injection must be administered only by a healthcare professional.”); PTX-133 at 4; PTX-162 at 4; PTX-595 at 6; Tr. 139:3-7 (Sommi). With only one actor, there is no divided infringement. Next, the Court turns to whether Mylan specifically intends to induce infringement.

3. *Mylan specifically intended to induce infringement*

In ANDA cases, induced infringement requires showing that the proposed labels “encourage, recommend, or promote infringement.” *Vanda*, 887 F.3d at 1129. Proposed labels induce infringement if they either “implicitly or explicitly encourage or instruct users to take action that would inevitably lead to” infringement. *See GlaxoSmithKline*, 7 F.4th at 1330. Here, Janssen proved inducement by presenting evidence that Mylan’s Proposed Labels explicitly instruct HCPs to practice the Asserted Claims, and inevitably lead HCPs to infringe the Asserted Claims.

a. The explicit instructions in Mylan’s Proposed Labels establish specific intent

Whether the Court infers specific intent “depends on how explicitly the instructions suggest the infringement, any direct evidence, the Court’s fact-finding conclusions and the surrounding

circumstances.” *Acorda Therapeutics Inc. v. Apotex Inc.*, Civil Action No. 07-4937, 2011 U.S. Dist. LEXIS 102875, at \*47 (D.N.J. Sep. 6, 2011), *aff’d*, 476 F. App’x 746 (Fed. Cir. 2012). “Depending on the clarity of the instructions, the decision to continue seeking FDA approval of those instructions may be sufficient evidence of specific intent to induce infringement.” *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1368 (Fed. Cir. 2017). “Proposed labeling that instructs [an] infringing use[] is generally sufficient to support a finding of intentional inducement.” *BTG*, 352 F. Supp. 3d at 399 (collecting cases).

Mylan’s Proposed Labels explicitly instruct HCPs to reinitiate patients onto PP3M in an infringing manner, by directing HCPs “[t]o manage missed doses.” Mylan’s Proposed Labels explicitly instruct HCPs to practice the Asserted Claims by directing HCPs to Section 2.3 “[t]o manage missed doses.” PTX-92 at 1; PTX-133 at 1; PTX-162 at 1; PTX-595 at 5; Tr. 120:5-9 (Sommi); Tr. 260:4-9 (Berger). Under Section 2.3’s subheading, “Missed Dose 4 Months to 9 Months Since Last Injection,” Mylan’s Proposed Labels instruct HCPs that, where the patient last received a PP3M dose four to nine months ago, “do NOT administer the next dose of [PP3M]. Instead use the re-initiation regimen in Table 2.” PTX-92 at 6-7; PTX-133 at 6-7; PTX-162 at 6-7; PTX-595 at 14-15. And Table 2, in turn, directs HCPS to perform all three administrating steps of the claimed re-initiation regimen. PTX-92 at 7; PTX-133 at 7; PTX-162 at 7; PTX-595 at 15.

Moreover, missed doses and patients returning between 4 and 9 months after a missed dose are inevitable, meaning that infringement of the claimed reinitiation regimen would be inevitable. Even Mylan’s expert, Dr. Berger, testified that Trinza/PP3M did not solve nonadherence among schizophrenia patients. Tr. 182:21-22 (Berger) (“No. It’s still a problem, still a big problem.”); Tr. 77:9-11, 107:25-108:1 (“So if this were a perfect world, then you wouldn’t have to have a missed dose section.”), Tr. 119:13-16 (Sommi); Tr. 873:13-874:1, 884:6-7 (Kohler)

(“[N]onadherence will occur again.”); *see also* PTX-1 at 2:20-24 (“Even with a drug administered once every 3 months . . . , patients at times miss their doses of medication.”). Dr. Berger acknowledged that “more than 50 percent” of Trinza patients have missed a dose, including “20 to 30 percent” returning for an appointment 16 or more weeks (about 4 months) after the missed dose. Tr. 251:1-14, 262:4-8, 310:12-18 (Berger).<sup>13</sup>

Dr. Kohler likewise testified that he had multiple patients who returned for a reinitiation dose of Trinza between 4 and 9 months after their last dose. Tr. 886:11-14, 888:18-24, 890:1-6 (Kohler).<sup>14</sup> Thus, even though the Trinza label advises that missed doses should be avoided, many patients still miss their PP3M doses, and inevitably return within 4 to 9 months for reinitiation.

And when they return, it is likewise inevitable that at least some HCPs will follow the instructions on Mylan’s Proposed Labels. Dr. Kohler testified credibly to having done so. Tr. 886:11-890:1-6 (Kohler). *see also* PTX-220 at 9 (“The vast majority of patients” were initiated onto Trinza “based on the prescribing guidelines.”).

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<sup>13</sup> On Re-direct, Dr. Berger testified that the “20 to 30%” could “include more than nine months” after the prior dose. Tr. 310:12-17. But Dr. Berger did not specify what percentage of that 20 to 30% was outside of the claimed 4 to 9-month window. The Court finds, based on Berger’s testimony and other credible testimony, that at least some percentage of PP3M patients would inevitably return between 4 to 9 months after their last missed dose.

<sup>14</sup> Mylan objected to Janssen using Dr. Kohler’s testimony to support Janssen’s infringement argument when he was called only for secondary considerations, and in light of Janssen’s numerous objections to Mylan’s infringement questions. Mylan Br. 25, n.11; Mylan Resp. Br. 27; Tr. 909:6-9, 927:19-20, 928:19-24, 929:11-13, 930:21-22, 933:25-934:3. As an initial matter, the Court notes that its direct infringement findings do not hinge solely on Kohler’s testimony—there is other evidence in the record, including Dr. Berger’s testimony, of inevitable infringement. Moreover, the Court agrees with Janssen that it can correct Mylan’s incorrect statement that “Janssen chose to forego any testimony from a prescribing physician who had or would follow the claimed missed-dose regimen.” Mylan Br. 25. Having placed the matter at issue by making this false assertion, Mylan cannot prevent Janssen from pointing out that the statement’s inaccuracy. And in any event, there is significant “overlap in the proofs required on the issues of validity and infringement.” *P&G v. Nabisco Brands, Inc.*, 604 F. Supp. 1485, 1492 (D. Del. 1985).

Dr. Berger testified that he does not use the claimed missed dose dosing instructions because providers should not “blindly follow the prescribing information.” Tr. 204:15-23, 231:9-21 (direct); 261:14-19 (cross). But even if this Court were to accept that testimony as credible, he nevertheless conceded that he had supervised medical residents who had “tried to reinitiate” patients on Trinza who had missed a dose between 4 and 9 months ago. Tr. 257:14-25 (supervising residents who consulted Trinza label when their patients missed PP3M 4-9 months ago); Tr. 264:24-265:4 (equating drug label to a speed limit and admitting that he himself follows the speed limit); *see also* Tr. 263:16-19 (Q: [S]ome health care providers do follow label instructions for patients who have missed a dose of PP3M by 4 to 9 months, right? A: I’m sure they try.”), 263:22-264:2 (Berger).

The Court simply cannot credit Dr. Berger’s testimony that not a single HCP would use the claimed reinitiation dosing regimen. But even if that testimony were credible, the standard is inevitable infringement, not universal infringement. Dr. Berger concedes that at least some have attempted it. In other words, upon a patient’s inevitable return between 4 and 9 months after a missed dose, it is inevitable that an HCP would at least attempt the claimed reinitiation regimen.

At least one other Mylan witness confirmed as much. Mylan’s Rule 30(b)(6) witness, Director of the North America Portfolio Development Team, testified that she “would assume [Mylan’s customers] are going to use [its product] according to the label that’s provided.” Reed Dep. Tr. 204:12-24. Reed also testified that “[Mylan] would provide the label with the product to [its] customers and . . . they can use it accordingly.” Reed Dep. Tr. 204:12-24. Because Mylan’s Proposed Labels instruct HCPs to use the Asserted Claims’ dosing regimens in an infringing manner, Mylan specifically intends for HCPs to use its Proposed ANDA Products in a way that infringes the Asserted Claims.



The Court is unpersuaded by Mylan's contention that its Proposed Labels discourage infringement by warning that missed doses should be avoided. Mylan Br. 28-29. This is essentially a repackaged version of Mylan's dual-actor divided infringement theory, rejected above, that a patient missing a dose is the Asserted Claims' first step. *See* Mylan Resp. Br. 24 (“[T]he label expressly discourages taking the first step, counseling that patients *should not* miss their doses.”) (emphasis in original).

Here, the Proposed Labels discourage missed doses, but do not discourage or make optional the practice of the Asserted Claims (or any claimed steps) in the inevitable situation that doses *are* missed. *See* Tr. 884:4-7 (Kohler) (“[P]eople who go on to [LAIs] for different reasons have been shown to have a high rate of nonadherence. So nonadherence will occur again.”); 1060:17 (Berger) (acknowledging that nonadherence is a common occurrence with Trinza); 1092-193 (Mulhern) (summarizing literature on schizophrenia patient/Trinza nonadherence); *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 352 F. Supp. 3d 352, 398 (D.N.J. 2018) (“The *only* way to follow these labels is to administer abiraterone, together with prednisone, in specified doses, to a mCRPC patient.”); *cf.* *Takeda Pharms. USA, Inc. v. West-Ward Pharm. Corp.*, 72 F. Supp. 3d 539, 547 (D. Del. 2014) (label instructed that the claimed method itself should be avoided); *cf.* *HZNP Meds. LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019) (one of the claimed steps was optional).

Nor is the Court persuaded by Mylan's argument that it does not induce infringement because its infringing instructions are not found in the “Indications and Usage” section of its Proposed Labels. There is no such requirement to prove induced infringement. *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018) (“When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, ‘the label must encourage, recommend, or promote infringement.’”) (cleaned up);

see also *Bayer Schering Pharma AG & Bayer HealthCare Pharm., Inc. v. Lupin, Ltd.*, 676 F.3d 1316, 1324 (Fed. Cir. 2012) (“[T]he point is that the label, *taken in its entirety*, fails to recommend or suggest to a physician that Yasmin is safe and effective for inducing the claimed combination of effects in patients in need thereof.”) (emphasis added).

4. *Allegedly noninfringing uses do not defeat infringement*

Mylan argues that its Proposed Labels cannot induce infringement because they contain numerous non-infringing instructions for PP3M. The Court disagrees.

There is “no legal or logical basis” for limiting induced infringement liability where a proposed label has substantial noninfringing uses. See *Sanofi v. Watson Lab’ys Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017). Where a drug label encourages infringement, a defendant “can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses.” *Sanofi*, 875 F.3d at 646 (citing *MGM Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 934 (2005); see also *Vanda*, 887 F.3d at 1133 (“[E]ven if the proposed ANDA product has ‘substantial noninfringing uses,’ [the ANDA applicant] may still be held liable for induced infringement.”); *Eli Lilly*, 845 F.3d at 1368-69 (“[A] label that instructed users to follow the instructions in an infringing manner was sufficient . . . even though the product in question had substantial noninfringing uses.”). Based on the Court’s finding that Mylan’s Proposed Labels will inevitably lead HCPs to infringe, Mylan induces infringement whether or not the Proposed Labels also contain noninfringing uses.

But Mylan’s arguments also fall short as a factual matter. Dr. Berger cited Mylan’s Proposed Labels §§ 2.6 and 2.7 as non-infringing alternatives. But as Dr. Berger conceded, these sections involve switching from PP3M to PP1M injectables (2.6) or PP3M to oral paliperidone (2.7). Tr. 214:25-215:5, 276:17-277:1, 281:7-9 (Berger). Neither is directed to patients who last

received PP3M 4 to 9 months ago. *Id.*; PTX-92 at 8; PTX-133 at 8; PTX-162 at 8; *see also* PTX-595 at 17. Thus, while Mylan’s generics may, and likely will, have non-infringing uses, there are no alternatives or non-infringing uses of the 4 to 9-month clinical presentation addressed by the Asserted Claims.

Accordingly, the Court finds that Janssen has demonstrated, by a preponderance of the evidence, that Mylan’s Proposed Labels will induce infringement of the Asserted Claims.

**B. OBVIOUSNESS: Mylan failed to prove through clear and convincing evidence that the asserted claims of the 693 Patent would have been obvious to a persona of ordinary skill in the art (“POSA”)**

In its defense, Mylan asserts that the Asserted Claims are invalid for obviousness, *i.e.* that the Asserted Claims would have been obvious to a POSA based on available prior art. The Court disagrees.

“A patent for a claimed invention may not be obtained ... if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a [POSA] to which the claimed invention pertains.” 35 U.S.C. § 103.

A party asserting a patent’s obviousness must prove “by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *Novartis Pharm. Corp. v. W.-Ward Pharm. Int’l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019). Obviousness is a question of law based on underlying facts, including: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill; and (4) objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

1. *The PP3M prior art was likely considered by the PTO Examiner*

Having been approved by the Patent Office, the Asserted Claims are generally presumed valid. 35 U.S.C. § 282(a); *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 110-14 (2011). Mylan argues, however, that no deference is owed to the PTO's issuance of a patent because certain PP3M prior art was not before the PTO's claim examiner: JAMA,<sup>15</sup> the 2014 Press Release,<sup>16</sup> and NCT 423.<sup>17</sup> Mylan Br. 49-50. Janssen counters that the challenger's overall burden to demonstrate invalidity by clear and convincing evidence remains unchanged.

Both are correct. Mylan is correct that "if the PTO did not have all material facts before it, its considered judgment may lose significant force." *i4i*, 564 U.S. at 111. But this does not change the challenger's burden; it simply means that the burden "may be easier to sustain." *Id.* Or phrased differently,

When new evidence touching validity of the patent not considered by the PTO is relied on, the tribunal considering it is not faced with having to disagree with the PTO or with deferring to its judgment or with taking its expertise into account. The evidence may, therefore, carry more weight and go further toward sustaining the attacker's unchanging burden."

*Id.* (citing *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360 (Fed. Cir. 1984)).

That said, a dispute about whether prior art was previously before the examiner may be evaluated by a factfinder in the context of the challenger's overall burden. *i4i*, 564 U.S. at 111. Here, the Court finds that the PTO examiner conducted prior art searches on the East and Google

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<sup>15</sup> Berwaerts et al., *Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia*, Journal of the American Medical Association ("JAMA") Psychiatry 72(8) (2015). PTX-113.

<sup>16</sup> Janssen Investigational Treatment for Schizophrenia Shows Positive Efficacy, Delays Relapse (2014). PTX-160.

<sup>17</sup> ClinicalTrials.gov archive, *History of Changes for Study: NCT01515423, Study of Paliperidone Palmitate 3 Month and 1 Month Formulations for the Treatment of Patients With Schizophrenia*. PTX-158.

Scholar databases. DTX-8 at 193. Although the search terms used on Google Scholar were apparently not recorded, the Examiner's search queries on East included "paliperidone," "three month," and the inventor names. *Id.* 205-06, 236-37. It is therefore likely that the Google Scholar search would have included any PP3M prior art. *See*, Tr. 691:2-7 (Forrest) ("assum[ing]" that Google Scholar would include JAMA).<sup>18</sup> However, even if the PTO Examiner did not consider all of the PP3M prior art, Mylan would nevertheless have failed to meet its burden.

2. *Mylan failed to prove that every element of the Asserted Claims was known in the prior art*

"An obviousness determination generally requires a finding that 'all claimed limitations are disclosed in the prior art.'" *Univ. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 160 (Fed. Cir. 2021) (quoting *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014)). But an "invention is not obvious simply because all of the claimed limitations were known in the prior art.'" *Forest Lab 'ys, LLC v. Sigmapharm Lab 'ys, LLC*, 918 F.3d 928, 934 (Fed. Cir. 2019). Instead, courts ask "whether there is a reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references." *Id.* (cleaned up). "The presence or absence of a motivation to combine" and what constitutes "a reasonable expectation

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<sup>18</sup> To the extent that Mylan argues that the Court must disregard such evidence, its citation to *Sun Pharma Glob. FZE v. Lupin Ltd.*, No. 18cv02213, 2021 U.S. Dist. LEXIS 42600 (D.N.J. Mar. 8, 2021), is inapposite. In that matter, the Court excluded testimony about an examiner's search history, but did not exclude the fact of the search or the exact query. *Id.* \*8-9. Where there is documentary evidence in the record, the Court may consider it. *See Elan Corp., PLC v. Andrx Pharm., Inc.*, No. 98-7164, 2008 U.S. Dist. LEXIS 94525, at \*284-85 (S.D. Fla. Aug. 12, 2008) (finding that "the Examiner presumably found the [prior art], determined that it was unimportant to the patentability of the [claimed invention], and chose not to cite it as material prior art."); *cf Comcast Cable Communs., LLC v. Sprint Communs. Co., LP*, 203 F. Supp. 3d 499, 547 (E.D. Pa. 2016) ("Expert testimony about the subjective knowledge or state of mind of the examiner is not admissible *in the absence of any support in the record.*") (emphasis added).

of success” are questions of fact. See *Novartis Pharms. Corp. v. West-Ward Pharms. Int’l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019) (cleaned up).

In assessing obviousness, factfinders “should be aware . . . of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). “Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.” *In re NTP, Inc.*, 654 F.3d 1279, 1299 (Fed. Cir. 2011) (internal quotation marks omitted).

Here, Mylan has failed to demonstrate that all claimed limitations were disclosed in the prior art, that a skilled artisan would have reason to combine the prior art references, and that the skilled artisan would have a reasonable expectation of success from doing so. The Court agrees with Janssen that Mylan’s obviousness case can best be characterized as a “hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013) (cleaned up). Mylan’s expert, Dr. Forrest, cherry-picked from the prior art; when one data point did not lead to the desired conclusion (the Asserted Claims’ reinitiation regimen), he chose another that did.<sup>19</sup>

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<sup>19</sup> Though the Court details disagreements with Dr. Forrest’s specific findings below, other general indicia undermined the persuasiveness of his testimony. Prior to his work in this case, Dr. Forrest had: never seen the 693 Patent, never worked with antipsychotics, no experience with treating psychotic disorders, never done any work that involved direct patient care, and no experience with paliperidone. Tr. 676:20-677:11 (Forrest). Mylan’s counsel provided copies of the references and the specific combinations that he relied on to support obviousness. Tr. 678:14-25 (Forrest). Dr. Forrest was retained in February 2022. Tr. 679:5-9 (Forrest). On March 9, 2022, weeks after being retained, Dr. Forrest signed a 189-page expert report that included a technical tutorial of PP; a description of the 693 Patent; an explanation of the 693 Patent’s prosecution history; a summary of 15-16 separate references; and a detailed basis for his invalidity opinions on obviousness, non-

Neither the PP3M references (JAMA, the 2014 Press Release, and NCT 423) nor the PP1M references (Invega Sustenna Label, the 536 Publication, the 519 Publication, and Samtani 2009) disclose or suggest the Asserted Claims' limitations. Mylan failed to prove that every element of the Asserted Claims was known in the prior art because, as a whole, they assert a unique combination of elements: (1) a missed dose regimen for PP3M; (2) administered to a specific patient population whose last dose of PP3M was 4 to 9 months ago; (3) treating a patient who had been advanced from PP1M to PP3M with PP1M reinitiation loading doses; and (4) returning the patient to PP3M treatment without first stabilizing the patient on PP1M for several months. Tr. 538:2-20 (Sommi).

As an initial matter, an exception to the general rule requiring a challenger to identify *all* claim limitations in the prior art is where the POSA's "common knowledge" may supply a *missing* limitation. *See Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1361-62 (Fed. Cir. 2016). But that exception applies only where "the limitation in question [is] unusually simple and the technology particularly straightforward." *Id.* at 1362; *accord Koninklijke Philips NV v. Google LLC*, 948 F.3d 1330, 1338 (Fed. Cir. 2020). And even then, "'common sense'...cannot be used as a wholesale substitute for reasoned analysis and evidentiary support." *Arendi*, 832 F.3d at 1362 (concluding that Board erred in relying on "common sense" based on "conclusory statements and unspecific expert testimony"); *Koninklijke*, 948 F.3d at 1338.

To the extent that Mylan argues that a POSA could have used "common sense" to arrive at the Asserted Claims' reinitiation regiment, Dr. Forrest relied entirely upon the prior art without

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enablement, lack of written description and indefiniteness. Tr. 679:5-680:2 (Forrest). In that time, he also "developed a PK model and ran simulations." Tr. 679:22-680:2 (Forrest). Just a few weeks later, on March 31, 2022, Dr. Forrest submitted another expert report on invalidity of two separate patents in a different patent litigation on a different drug involving a completely different disease, *i.e.*, heart failure. Tr. 680:8-681:12 (Forrest).

mention of “common sense.” *See, e.g.*, Tr. 474:7-475:15 (Forrest); Forrest Demonstratives Slide 6 (“The prior art renders obvious the asserted claims of the ‘693 patent[.]”); *id.* at Slide 43 (“The Approach to Missed Doses for PP3M Was Taught by the Prior Art.”). “Common sense” or “common knowledge” were not mentioned at trial. To the extent that Dr. Forrest’s testimony regarding “routine optimization” is meant to represent a POSA’s “common sense,” his testimony was too vague to supply missing claim limitations.

But even if the testimony regarding “common sense” had been more robust, “common sense” cannot be used to lead a POSA to develop missing elements of the claim because the missing elements are not “unusually simple” or the technology at issue “particularly straightforward.” Tr. 555:16-22 (Sommi) (PP1M pharmacokinetics “were rather complicated and complex and very different from what we had up until that point ... applying simple math probably wasn’t going to work.”), 848:15-19 (Gobburu) (“If you change the formulation” from PP1M to PP3M, you “cannot predict the pharmacokinetics of the new formulation.”); *see Sanofi-Aventis Deutschland GmbH v. Glenmark Pharm. Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) (“[I]n the medical arts potential solutions are less likely to be genuinely predictable, as compared with other arts such as the mechanical devices in KSR.”) (cleaned up). Thus, Mylan has failed to demonstrate obviousness.



Dr. Forrest relied primarily on four PP1M prior art references: the Sustenna label,<sup>20</sup> the 536 Publication,<sup>21</sup> the 519 Publication,<sup>22</sup> and Samtani 2009.<sup>23</sup> None referenced PP3M; rather, the thrust of Dr. Forrest's testimony (and Mylan's obviousness case) is that PP1M prior art could be extrapolated to determine the Asserted Claims' PP3M reinitiation dosing regimen. For the reasons below, Dr. Forrest's testimony evidenced hindsight-driven reverse engineering, not obviousness. Dr. Forrest cherry-picked PP1M data to arrive at his desired conclusion about PP3M.

a. The Sustenna label

First, Dr. Forrest extrapolated from the Sustenna Label, PTX-106, to estimate the front end of the intermediate window ("[m]ore than 6 weeks to 6 months since last injection") for a PP3M missed dose regimen. PTX-106 at 4-6 (§ 2.3); Tr. 705:2-5 (Forrest). Dr. Forrest noted that the front end of the Sustenna intermediate window started at six weeks, or about 1.4 times the one-month dosing interval of PP1M (30 days). Tr. 707:12-18 (Forrest); Tr. 558:9-10 (Sommi). Dr. Forrest then applied the 1.4x multiplier to PP3M's dosing interval (90 days), and calculated 4.2 months (126 days) as the front end of the intermediate missed dose window for PP3M. Tr. 707:12-18 (Forrest); Tr. 558:9-14 (Sommi). Dr. Forrest concluded that 4.2 months was "approximately" the 4 months recited in the 693 Patent claims. Tr. 707:23-708:2 (Forrest).

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<sup>20</sup> Invega Sustenna Prescribing Information (Rev. 11/2014). PTX-106.

<sup>21</sup> The 536 Publication (US 2011/0105536) is "Dosing Regimen Associated with Long-Acting Injectable Paliperidone Esters." PTX-116 at 1. It taught that simulating missed dose scenarios using PK models could be used to design PP1M missed dose regimens, but does not disclose PP3M dosing regimens. PTX-116 ¶ [0088]; *see also* Figs. 2 and 3; Tr. 435:25-436:2 (Forrest).

<sup>22</sup> A patent application publication of US 2009/0163519, "Dosing Regimen Associated with Long-Acting Injectable Paliperidone Esters," relating to PP1M PTX-115 at 1; Tr. 414:16-21 (Forrest).

<sup>23</sup> Samtani et al., *Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia: A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic*, Clin. Pharmacokinet 48(9) (2009): 585-600. PTX-118.

The problem with Dr. Forrest's approach is its inconsistency: when the same extrapolation arrived at different results, he simply ignored them. As Dr. Forrest admitted, if the same logic used on the front end were applied to the back end, a POSA would—at least initially—arrive at 18 months on the back end of the window. Tr. 710:13-25 (Forrest); Tr. 558:20-559:7 (Sommi) (back end of PP1M intermediate window is 6 months, or 6 times the monthly dosing interval; multiplying the PP3M dosing interval by 6 is 18 months). In other words, the same theory would set the back of the PP3M intermediate window at 18 months, “about twice as long” as the 9-month back end recited in the Asserted Claims. Tr. 559:10-13 (Sommi). And the data would refute the theory.

Dr. Forrest's credibility was undermined by his evasive responses on cross-examination when confronted with this inconsistency. Tr. 709:16-711:20 (Forrest) (“Q. Well, applying your own logic then, you would calculate the back end of the intermediate window for PP3M to be 18 months, right?” A. ...Let me say no, that I would need to explain further.”; “Q. At your deposition, ... I asked you the question, ‘And if you applied it to the back end, you would get to about 18 months, or about 540 days.’ You said yeah. You’re replying that, of course, as I discussed in my report, would see there it would be potentially that long. Right? A. Yes.”). The Court is persuaded by the testimony of Drs. Sommi and Gobburu, who both explained that a POSA would not have relied on simple extrapolation of PP1M data to arrive at conclusions about PP3M pharmacokinetics, or applied the extrapolation so inconsistently. *See* Tr. 558:15-560:1 (Sommi); Tr. 813:9-12, 814:16-19 (Gobburu).

b. 4-5 Half-Life extrapolation theory

Dr. Forrest posited a different theory based on drug half-life. Tr. 711:22-25 (Forrest). The premise, relying on the 536 Publication, is that it takes about 4-5 half-lives for a drug to be completely eliminated. PTX-116 ¶ [0103]. This, the theory goes, would reveal the back end of

the intermediate window because that is when drug has been essentially eliminated from the patient's blood stream. Tr. 712:2-9 (Forrest); Tr. 560:2-21 (Sommi). The Court is persuaded that a POSA would not have relied on a 4-5 half-life theory, or any theory based on half-life to identify only one end of the window. Tr. 559:19-560:1, 586:18-24 (Sommi). A POSA would have known this assumption to be scientifically unreasonable, and instead "would have used the actual data," *i.e.*, PP3M's actual half-life data. Tr. 560:22-24, 563:11-22 (Sommi), 712:12-14 (Forrest).

However, the half-life of PP3M was not known in the prior art. Tr. 712:25-713:3 (Forrest); Tr. 560:25-561:3 (Sommi). Instead, Dr. Forrest did what a POSA would not have: assumed that PP3M's half-life could be extrapolated from PP3M's dosing interval (every 3 months). Assuming the half-life for PP1M was 30 days (based on its dosing interval), Dr. Forrest multiplied that by three to assume a PP3M half-life of 90 days. Tr. 713:17-20, 717:21-23 (Forrest). That assumption was wrong: PP3M's actual half-life, reported *after* the Patent's filing date, is approximately 120 to 140 days, or 4-4.5 months. PTX-192 at 6; Tr. 817:24-818:6, 861:8-14 (Gobburu); Shaw Dep. Tr. 136:9-12<sup>24</sup> ("[W]ithout measuring the blood levels, you cannot predict what the half-life of Mylan's proposed PP3M is.").

There were other issues with this approach beyond its objective inaccuracy. PP1M's measured half-life was disclosed in the 519 Publication, which taught that PP1M's half-life was "dose-related," Tr. 562:21-25 (Sommi), increasing "from 25 days (median) after the 25 mg eq. dose to 40-49 days (median) after the 100 and 150 mg eq. dose, for both injection sites." PTX-115 ¶ [0098]; *see* Tr. 713:14-16 (Forrest). In assuming that PP1M's half-life was uniformly 30 days, Dr. Forrest ignored the reported, dose-dependent half-life of PP1M. Tr. 563:1-7 (Sommi).

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<sup>24</sup> Dr. Andrew Shaw, Mylan's 30(b)(6) witness.

Dr. Forrest relied on an observation in the 536 Publication that “[t]he results in Table 3 showed that, for all depot antipsychotics, the administration interval was in the range of about 1-2 half-life for each product.” PTX-116 ¶ [0103]; Tr. 714:1-5 (Forrest). There are several scientific flaws with this.

First, it ignores that PP1M’s actual half-life is not 30 days, but between 25 and 40 to 49 median days depending on dosage. Tr. 717:11-13 (Forrest) (acknowledging as high as 49 days); PTX-115 (519 Publication) ¶ [0098].

Second, even if a POSA were to use the 536 Publication’s statement to estimate a half-life for PP1M, it would teach that the 30-day dosing interval for PP1M would be 1-2 half-lives, meaning that 1 half-life would be anywhere from 15 to 30 days for PP1M—again, inconsistent with PP1M’s *actual* half-life of 25 to 49 days. Tr. 717:6-13 (Forrest); Tr. 561:9-19 (Sommi).

Third, Dr. Forrest testified on direct that the 536 Publication was “all about paliperidone palmitate.” Tr. 430:4-6 (Forrest). But the 536 Publication’s half-life observations, set forth in its Table 3, were expressly *not* about PP, but “a literature search [that] was conducted to evaluate the pharmacokinetic characteristics of *other* long acting injectable antipsychotics.” PTX-116 ¶ [0102] (emphasis added). The “authors made an observation that there was a relationship between the administration interval and the half-life” for the products listed in Table 3, which did not include PP. Tr. 561:11-14 (Sommi). Confronted with this on cross-examination, Dr. Forrest evaded. *See* Tr. 713:23-715:10 (Forrest).

Utilizing these imperfect data points, Dr. Forrest then multiplied the purported 30-day half-life of PP1M by three and assumed the half-life of PP3M would be about 90 days. Tr. 717:21-23 (Forrest); Tr. 561:9-19 (Sommi). Dr. Forrest then applied his 4-5 half-life theory to calculate the

back end of the intermediate window for PP3M to be at about 12-18 months. Tr. 464:24-465:6 (Forrest); Tr. 564:8-15 (Sommi).

c. Dr. Forrest's JAMA<sup>25</sup> "natural jump" theory

Before trial, Dr. Forrest relied on a PK modeling exercise to identify the back end of the intermediate missed dose window for PP3M as 9 months. Tr. 720:2-6 (Forrest). But at trial, Dr. Forrest unveiled a new theory: that a POSA could have used JAMA to arrive at the 9-month target, and that his PK modeling was only used to validate the conclusion reached under this new theory. Tr. 509:2-4 (Forrest).

Dr. Forrest's JAMA theory relies on the Kaplan-Meier plot of JAMA's Figure 2A, which plots interim data analysis. Then, notwithstanding the author's express conclusion that the plot shows the median relapse time to be 274 days after randomization, *i.e.*, 12 months since the last PP3M injection, a POSA would make a "natural jump" backwards, to 180 days after randomization, *i.e.*, 9 months since the last PP3M injection, as the intermediate window's back end. Tr. 465:14-468:22 (Forrest).

Dr. Forrest's testimony on this was not credible for a few reasons. First, relying on the theory requires exclusive reliance on JAMA's interim analysis to the exclusion of any additional data collected as part of JAMA's final analysis, which evidenced a 395-day (16-month) relapse time after the last PP3M dose. Tr. 703:24-704:4 (Forrest); Tr. 549:9-11 (Sommi); PTX-113 at 4. Dr. Forrest's testimony that "JAMA told us to ignore [the final analysis] data" is not credible based on his own testimony elsewhere that a POSA would "use all the data ... at hand." Tr. 720:1; Tr. 720:10-12 (Forrest) ("You would put the appropriate weight on each one and understand which is

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<sup>25</sup> Berwaerts et al., *Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia*, Journal of the American Medical Association ("JAMA") Psychiatry 72(8) (2015). PTX-113.

most relevant, but you would use data that is available.”). Not once could Dr. Forrest credibly explain why a POSA would use all data in the prior art *except for* JAMA’s final analysis. Tr. 720:13-721:13 (Forrest).

That is because a POSA *would* use all data. Tr. 547:17-19 (Sommi). JAMA’s interim analysis was conducted because JAMA was a relapse prevention trial involving schizophrenia patients who received placebo; because of “a risk of relapse,” interim analysis is conducted for ethical reasons to determine whether to unblind the study early. Tr. 546:4-547:6 (Sommi). But “[w]hen they say the study is over, it may take three, four, five, six months to get all the patients out of the study safely,” during which they are “still collecting data.” Tr. 547:11-16 (Sommi); PTX-113 at 3 (“Results through the end of the DB phase after early termination of the study (i.e., cumulative data including those from before the interim cutoff data) are reported herein as the final analysis . . . .”). There is no reason, from a POSA’s perspective, not to consider all data available.

Second, JAMA’s interim (and final) analyses were based on measuring delay of time to relapse, meaning hospitalization or a PANNS score<sup>26</sup> increase. Tr. 543:13-22 (Sommi); Tr. 692:6-11 (Forrest). Neither is a precise pharmacokinetic outcome measuring PP plasma concentration. Tr. 543:23-25 (Sommi). More importantly, Dr. Forrest lacks the expertise to opine on clinical considerations. Tr. 676:23-677:4, 1191:1-2 (“I am not a clinician.”) (Forrest). But Dr. Sommi, a Board-certified psychiatric pharmacist with extensive clinical psychiatric experience, testified credibly that a POSA would not have adopted Dr. Forrest’s approach of extrapolating the intermediate window for a missed dose regimen from JAMA’s relapse data, or at least would have

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<sup>26</sup> Positive and Negative Syndrome Scale (PANSS) for Schizophrenia measures the prevalence of positive and negative syndromes in schizophrenia; for example, self-injury, violent behavior, or aggression. Tr. 543:15-22 (Sommi).

incorporated the 395-day relapse datum from the final analysis. Tr. 46:1-50:2, 50:3-51:24, 545:11-546:3, 547:10-11, 548:16-594:14 (Sommi); PTX-113 at 4.

Third, Dr. Forrest never adequately explained the “natural jump.” Janssen, however, offers a plausible explanation: the “jump” was simply Dr. Forrest changing his opinion when confronted with an inconsistency. At his deposition, Dr. Forrest testified that JAMA directly taught that the relapse time from randomization<sup>27</sup> was 274 days (9 months), *i.e.*, the Asserted Claims’ back end. Tr. 550:18-20. The problem? Dr. Forrest did not factor in that patients had received a PP3M dose 3 months *before* randomization, meaning that—using Dr. Forrest’s theory—JAMA actually taught a 12-month back end.

And finally, the JAMA theory also suffers from the same selective-application defect discussed above. Dr. Forrest did not attempt to use JAMA to calculate the front end. Tr. 550:25-551:2 (Sommi). And for good reason; even if JAMA’s interim data *could* be used to correctly discern the intermediate window’s back end (9 months), using the same method would have revealed a 6-month front end, not the actual 4-month front end borne out by the data and found in the Asserted Claims.

d. Samtani 2009<sup>28</sup>

Dr. Forrest testified that he relied on Samtani 2009 to build PP1M and PP3M PK models, which he used to run Excel simulations. Tr. 480:1-4, 502:18-23, 722:11-13 (Forrest); Tr. 587:10-13 (Sommi). Samtani 2009 “describes the population pharmacokinetic modeling of PP1M formulation.” Tr. 820:20-23 (Gobburu). Samtani 2009 discloses a PP1M model developed

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<sup>27</sup> “Randomization” refers to the time that patients were placed into one of two groups: those receiving a placebo and those continuing on PP3M. Tr. 548:16-549:3.

<sup>28</sup> “Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia: A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic.” PTX-118 at 1; Tr. 843:11-19 (Gobburu).

through a pop-PK analysis, based on, and validated with, nearly 16,000 pharmacokinetics samples from about 1,400 PP1M patients. Tr. 566:21-25 (Sommi); Tr. 724:19-22 (Forrest). Samtani 2009 does *not* mention PP3M, and thus does not report any PP3M data. Tr. 724:16-18 (Forrest), 820:24-25 (Gobburu). This theory, too, attempted to extrapolate PP3M's PK from PP1M data—with the same result.

*i. Dr. Forrest selectively utilized just a few parameters influencing PK*

A POSA would not have built a PP3M PK model using PP1M data gleaned from Samtani 2009, nor would they have used the model to simulate dosing scenarios for PP3M. Tr. 573:11-18 (Sommi); Tr. 813:10-12, 814:16-815:1 (Gobburu). But even if a POSA had attempted that, Samtani 2009 taught that “antipsychotics are rife with inter-patient and intra-patient variability, so the pop-PK takes lots of different factors into account.” Tr. 567:21-25 (Sommi). Table III in Samtani 2009 identified 25 such parameters. Tr. 725:2-6 (Forrest); Tr. 821:6-11 (Gobburu).

Among those parameters, Samtani 2009 concluded that the PP's PK is mostly influenced by BMI (body mass index), CLCR (creatinine clearance), INJS (injection site), IVOL (injection volume), and NDLL (needle length). Tr. 568:9-22 (Sommi), 725:7-14 (Forrest); PTX-118 at 1. These parameters, and others, explain the “variability between patients” in how they respond to PP. Tr. 822:3-11 (Gobburu); PTX-145 at 491 (“Substantial differences in response to drugs commonly exist among patients.”).

But Dr. Forrest used only 4 of 25 parameters: CL (clearance), Vd (volume of distribution), Ka shift factor for deltoid injection, and the Ka (absorption rate constant). Tr. 725:15-25 (Forrest); Tr. 569:10-15 (Sommi). Dr. Forrest ignored “the variability between patients” where “the range of the blood levels . . . is dictated by whether the patient is a female or is a male . . . [or] is obese or nonobese.” Tr. 822:3-11 (Gobburu). Dr. Forrest agrees that a POSA would have understood



this variability. Tr. 724:23-725:1 (Forrest). But a POSA would not have extrapolated PP1M PK data to PP3M, and if attempting to do so, a POSA would have utilized *every* parameter known to influence PP1M PK. Tr. 813:13-16, 821:20-822:11 (Gobburu); cf Tr. 720:1 (Forrest) (“You use all the data you had at hand.”). Dr. Forrest did not. Tr. 567:12-15 (Sommi), 820:8-10 (Gobburu).

*ii. Dr. Forrest’s model ignored PP1M’s complex absorption*

Samtani 2009 teaches that “a dual absorption pharmacokinetic model best described the complex pharmacokinetics of [PP1M].” PTX-118 at 1; Tr. 570:9-12 (Sommi). This reflects PP1M’s “biphasic” absorption. Tr. 727:19-21 (Forrest); Tr. 570:9-16 (Sommi). The dual absorption model “is rather more complex than the simplified [model] that was used by Dr. Forrest.” Tr. 821:20-822:2 (Gobburu).

Dr. Forrest acknowledges that a biphasic absorption process has an initial zero-order component, Tr. 727:22-24 (Forrest), through which “a fraction of the dose  $f_2$  is absorbed relatively quickly.” PTX-118 at 1; Tr. 728:4-6 (Forrest). “[T]he zero order process really talks about where the concentration goes up really quickly. That’s a burst of concentration.” Tr. 570:17-22 (Sommi). Following the zero-order process, there is a first-order process that “allows that drug to be given over a longer period of time.” Tr. 570:23-571:6 (Sommi).

Forrest admitted that PP3M’s absorption, like PP1M’s, “could also be divided biphasically.”<sup>29</sup> Tr. 728:10-13 (Forrest). But Dr. Forrest’s models focused only on the elimination phase, using only a simple first-order equation for both PP1M and PP3M. Tr. 728:14-729:7, 742:23-24; Tr. 784:16-19 (Forrest) (“I wasn’t trying to count from the very beginning because that’s not very important for re-dosing”); Tr. 571:13-19 (Sommi). According to Dr. Forrest, he

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<sup>29</sup> Biphasic/dual absorption comprises zero order kinetics, the “burst of concentration” that “goes up really quickly” after injection, and first order kinetics, the “really ... slow absorption that accounts for why [PP1M or PP3M] could be given every one or three months.” Tr. 570:14-571:6.

did not include a zero-order absorption “because that was such a minor component.” Tr. 514:19-21, 729:3-10 (Forrest) (“Yes, 17%”). But, as Dr. Sommi credibly explained, a POSA would have understood that 17% of the drug being absorbed through the zero-order initial burst was not “minor,” but “about somewhere between the fifth and the sixth of the dose, ... a pretty significant amount.” Tr. 571:7-12 (Sommi). A POSA would have found Dr. Forrest’s approach “unscientific” because he focuses only on “a sliver of time window and ignor[es] the rest.” Tr. 827:11-15 (Gobburu).

*iii. Dr. Forrest extrapolates PP3M’s absorption rate (Ka) from PP1M*

For Dr. Forrest’s simple first order model to work, Dr. Forrest needed an absorption rate constant (“Ka”) for PP3M. Tr. 735:15-18 (Forrest). But PP3M’s Ka was not known in the prior art. Tr. 574:10-14 (Sommi); Tr. 815:2-7 (Gobburu). So, Dr. Forrest extrapolated PP1M’s Ka from Samtani 2009’s PP1M model and divided it by three. Tr. 735:19-736:5 (Forrest) (“[PP3M] is meant to last three times longer, so one third absorption rate is an estimate.”); Tr. 574:15-20 (Sommi); Tr. 815:17-18 (Gobburu).

But Dr. Forrest’s extrapolation was not reasonable. Samtani 2009’s PP1M Ka was based on a pop-PK model that accounted for biphasic absorption; it could not be plugged into a simple first-order model. Tr. 573:15-22, 574:21-575:1 (Sommi). A POSA would have known that “the pharmacokinetics of PP1M at least were rather complicated and complex and very different from what we had up until that point in the market. ...[S]imple math probably wasn’t going to work.” Tr. 555:16-22 (Sommi).

Dr. Gobburu agreed that this approach was “unscientific.” Tr. 802:23-804:7, 813:9-12 (Gobburu) (“The use of [PP1M] data to extrapolate to [PP3M] data is not based on science.”). Tr. 813:10-12 (Gobburu). “If you change the formulation” from PP1M to PP3M, you “cannot predict

the pharmacokinetics of the new formulation.” Tr. 848:15-19 (Gobburu); Shaw Dep. Tr. at 136:4-8 (“[W]ithout measuring the blood level, you wouldn’t know in any way . . . what Mylan’s proposed PP3M PK profile would look like.”). Thus, a POSA would not have had a reasonable expectation of success in following Dr. Forrest’s approach and extrapolating the absorption characteristics of PP3M from data about PP1M. Tr. 815:5-20 (Gobburu); Tr. 555:25-556:4 (Sommi).

But the data undermines that approach’s validity. Dr. Forrest posited a simple equation for doing so: “the half-life is related to the natural log of two divided by the  $K_a$ .” Tr. 489:25-490:1 (Forrest); Forrest Demonstratives Slide 54; *see also* Tr. 576:3 (Sommi) (“So half-life equals 0.693 divided by  $K_a$ .”). Based on the  $K_a$  Dr. Forrest used for modeling a PP3M injection in the gluteal muscle (0.003904), the half-life of PP3M would be 179 days. Tr. 737:25-738:14, 739:18-22 (Forrest). This is nearly twice as long as the PP3M half-life that he assumed for his 4-5 half-life theory—90 days. Plugging Dr. Forrest’s PP1M  $K_a$  (0.0117) into the same equation reveals the same issue: a 60-day half-life, twice the 30-day half-life Dr. Forrest assumed in his 4-5 half-life theory, and more than the longest known half-life of PP1M, *i.e.*, 49 days. Tr. 576:3-577:3, 577:4-9, 593:13-19 (Sommi).

Dr. Forrest attempted to explain a distinction between half-life for multi-dose versus single-dose injections. Tr. 738:11-16 (Forrest). But Dr. Gobburu credibly explained that the “half-life of a drug . . . is constant over single to repeated dosing in patients. So the half-life would remain the same for paliperidone absorption.” Tr. 818:15-819:14 (Gobburu).

*iv. Dr. Forrest’s “validation”*

To validate their PP1M pop-PK model, Samtani 2009’s authors used data from two different clinical studies, “includ[ing] 394 (21.9%) subjects who contributed to 2776 (15%) plasma

samples.” PTX-118 at 2. Conversely, Dr. Forrest used a handful of median plasma concentration data points for only one PP1M dose (the 100 mg eq. dose) extracted from Figure 1a of Samtani 2009. Tr. 506:9-22 (Forrest). But as Dr. Gobburu credibly explained, “there is a discordance between when the actual data ... rise up to the peak versus when the [projected concentrations] raises up to its peak, and the difference in simple terms between the two is about eight days,” or “more than 25%” of the 28-day cycle. Tr. 825:16-826:17 (Gobburu); Gobburu Demonstratives Slide 15.

Dr. Forrest relied on that model to project that plasma concentrations would reach or drop below the therapeutic window minimum (7.5 ng/mL) at 9 months to set the back end of the dosing window (as in the Asserted Claims). Tr. 512:25-513:7 (Forrest); Tr. 584:1-7 (Sommi). But again, Dr. Forrest’s data is selective: he picked only the 350 mg eq. dose of PP3M to simulate in his model, not the other three (175, 263, and 525 mg eq.). Tr. 740:13-26 (Forrest).

A POSA would have simulated them all if the doses were known, or at least simulated 525 mg eq., the highest dose. Tr. 580:23-582:12 (Sommi); *see also* PTX-192 at 55 (“[REDACTED]”); [REDACTED]”); PTX-161 (Samtani 2011), “Dosing and Switching Strategies for Paliperidone Palmitate: Based on Population Pharmacokinetic Modelling and Clinical Data” (teaching that PP1M’s highest dose had been used to select PP1M’s reinitiation regimen). The reason for this, as a POSA would know, is that “people with the highest dose are going to have the highest leftover concentrations.” Tr. 581:5-581:11 (Sommi). “[I]f you don’t get it right . . . and you restart [the regimen], they’ve got too much left, you run the risk of overshooting your target concentration and you get side effects.” Tr. 581:12-20 (Sommi).

If Dr. Forrest *had* simulated the highest 525 mg eq. dose, the back end of the dosing window would have been “at some point in time after the nine months.” Tr. 581:9-11, 584:8-15 (Sommi). Conversely, if Dr. Forrest had simulated a dose smaller than 350 mg eq., the time to cross the 7.5 ng/mL therapeutic minimum threshold would have been sooner than 9 months. Tr. 584:22-24 (Sommi).

3. *Mylan failed to prove motivation to combine prior art to arrive at the Asserted Claims with a reasonable expectation of success*

- a. Mylan did not prove any motivation to treat the 4-9 month missed dose patient population with a reasonable expectation of success

Dr. Forrest attempted to identify the 4-month front end of the dosing window using multipliers extrapolated from the Sustenna Label, and JAMA to arrive at the 9-month back end—neither credibly, as discussed above. A POSA would have had no reasonable expectation of success in extrapolating in this manner, but would have at least analyzed the front and back end in the same way. Tr. 558:15-560:1 (Sommi). Dr. Forrest’s inconsistent approaches to the data evidence his hindsight-driven approach; in other words, not an approach a POSA would have used, much less one with a reasonable expectation of success. Indeed, Dr. Forrest admitted that this is tantamount to “guessing.” Tr. 709:11-14 (Forrest).

- b. Mylan did not prove any motivation to use, or a reasonable expectation of success in combining the elements of the prior art

Even if Mylan could prove that the Asserted Claims were disclosed in the prior art, Mylan has also failed to prove by clear and convincing evidence that a POSA would have had a motivation or reason to combine elements of the prior art to arrive at the Asserted Claims’ reinitiation dosing regimen with a reasonable expectation of success. *In re Cyclobenzaprine*, 676 F.3d at 1068-69.

The 693 Patent was the first LAIA that recommended using two different long-acting injectable formulations to manage a missed dose. Tr. 557:14-17 (Sommi). The Sustenna Label

instructs to “resume the same dose [of Sustenna] the patient was previously stabilized on.” Tr. 556:19-557:6, 589:18-21 (Sommi); PTX-106 at 5. For PP1M missed doses, patients are reinitiated with PP1M (not a different formulation), Tr. 704:21-705:5 (Forrest), at the same dose that was missed (except for the highest dose), Tr. 705:9-13 (Forrest). There was nothing obvious, in other words, about using a non-PP3M formulation to reinitiate a patient that had been advanced to PP3M. Tr. 555:5-7 (Sommi); Tr. 741:7-12 (Forrest) (“the prior art just teaches giving PP1M, then PP3M”).

Indeed, even Dr. Berger—who has 50 years of clinical experience with antipsychotics, Tr. 159:14-23—agrees with Dr. Sommi, testifying that “before [J]Trinza came out” (*i.e.*, before the effective filing date of the 693 Patent), treating a patient who had missed a PP3M dose with PP1M catch-up doses would have been “a bad idea” that was “unsafe,” “unreasonable,” and/or “unwise.” Tr. 262:9-263:9, 1048:9-22 (Berger).<sup>30</sup>

Dr. Forrest argued that the Asserted Claims’ reinitiation regimen was obvious because a POSA would have known that PP1M is “faster acting” and “it was known that a PP1M could be used to load them up with drug pretty rapidly so they would be in steady state range for their repeat injections.” Tr. 413:20-414:3; Tr. 741:13-18 (Forrest). But Dr. Forrest was unable to point to any credible evidence that taught that PP1M reaches therapeutic levels any faster than PP3M. Tr. 742:5-11 (Forrest).

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<sup>30</sup> Dr. Berger later clarified that he did not mean it was unsafe “in all instances,” he nevertheless reiterated that it was “far safer” and “far wiser” to reinitiate nonadherent patients directly on PP3M rather than by using the dosing regimen of the Asserted Claims. Tr. 1043:5-24 (Berger). In other words, Dr. Berger—who rightly emphasized his 50 years of experience as a psychiatric practitioner—saw no reason to use PP1M after a patient has been advanced to PP3M, and had no reasonable expectation of success in doing so. This merely bolsters Janssen’s point that reinitiating patients who missed PP3M doses with PP1M was not obvious.

Dr. Forrest suggested that PP1M is faster-acting because PP3M may include larger particle sizes that are slower to absorb. Tr. 400:25-401:5, 406:19-407:3, 410:9-12 (Forrest). But that “would account for the back end of why you can dose this drug for three months,” not what happens at the initial burst. Tr. 594:16-595:7 (Sommi) (“We don’t know anything about the initial release.”). Indeed, Dr. Forrest’s flawed modeling suggests identical PP1M and PP3M absorption. Tr. 592:14-17 (Sommi), 828:15-25 (Gobburu); PTX-100D at 2.

Dr. Forrest admitted as much. Tr. 745:8-746:3, 746:18-25, 748:6-10 (Forrest); PTX-100D at 2. And this was true even though his comparison was skewed to favor faster absorption of PP1M by comparing the projected concentrations following 100 mg eq. of PP1M in the *deltoid* muscle versus 350 mg eq. of PP3M in the *gluteal*. Tr. 596:2-9 (Sommi). But deltoid injections result in a faster initial plasma concentration rise than gluteal injections, facilitating a more rapid attainment of therapeutic concentrations. Tr. 726:25-727:2, 747:15-20 (Forrest); Tr. 596:2-4 (Sommi); Tr. 829:6-8 (Gobburu). Dr. Forrest “could have modeled PP1M deltoid to PP3M deltoid,” but did not. Tr. 596:2-9 (Sommi). If he had, the initial concentration rise for PP3M “would have been faster,” Tr. 749:10-14 (Forrest), undermining Dr. Forrest’s assumption that PP1M is “faster acting.” Tr. 829:13-17 (Gobburu).

As Drs. Gobburu and Sommi explained, since the art lacked PK data about PP3M, a POSA would have had no reason to believe that PP1M would reach therapeutic concentrations faster than PP3M when used for reinitiation. Tr. 593:24-594:13 (Sommi); Tr. 827:24-828:10 (Gobburu); Shaw Dep. Tr. 136:9-12. Nothing in the prior art would have motivated a POSA to use PP1M after a patient advanced to PP3M. Tr. 598:11-13, 598:16-17 (Sommi). Nor would there have been any reasonable expectation that PP1M would reach therapeutic levels more rapidly than PP3M. Tr. 593:24-594:9, 598:18-21 (Sommi). Thus, a POSA relying on Dr. Forrest’s modeling-based

approach would have had no reason or motivation to reinitiate PP3M patients in an intermediate time window using PP1M, and, if anything, would have dissuaded from using PP1M. *See* Tr. 829:13-22 (Gobburu).

Other prior art bolsters this point. For example, patients missing an injection of Abilify Maintena, a different LAIA, received a Maintena injection supplemented with oral Abilify. Tr. 590:21-591:9 (Sommi); PTX-168 at 3-4. The Risperdal Consta label, another LAIA, likewise instructed administration of a missed Risperdal Consta injection supplemented with oral antipsychotic, and taught using this approach when “there are no data to specifically address reinitiation of treatment.” Tr. 591:10-18 (Sommi); PTX-187 at 7.

- c. Mylan did not prove any motivation to use, or a reasonable expectation of success in using, PP1M to reinitiate PP3M

There was also no motivation to use PP3M without first stabilizing the patient for four or more months on PP1M. Every PP3M reference relied on by Dr. Forrest required patients to be stabilized on PP1M for at least 4 months before advancing to PP3M. In the placebo-controlled study—as described in JAMA and the 2014 Press Release—all patients were stabilized on PP1M for 17 weeks before advancing to PP3M. Tr. 542:3-9, 553:10-15, 645:18-21 (Sommi). Similarly, in the study that compared PP3M to PP1M—as described in NCT 423—“[e]verybody was given PP1M” for 17 weeks to be stabilized on PP1M before half the patients advanced to PP3M. Tr. 541:11-18 (Sommi).

Thus, if a patient who missed a dose of PP3M were given PP1M, there would have been no reason or motivation to advance them to PP3M without first stabilizing them on PP1M for at least 17 weeks, since that was the only way PP3M was reportedly used in the prior art. *See* Tr. 686:2-14 (Forrest).



4. *Objective indicia of the Asserted Claims' nonobviousness*

Objective indicia of nonobviousness, or real-world facts related to the invention, also known as “secondary considerations,” are “essential safeguards that protect against hindsight bias” in the obviousness analysis. *Liqwd, Inc. v. L’Oreal USA, Inc.*, 941 F.3d 1133, 1136-37 (Fed. Cir. 2019); *see also WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (“The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis.”). Long-felt but unmet need for the patented technology, the commercial success of a product embodying that technology, and skepticism that the invention will work are all recognized as objective evidence that the claimed inventions are nonobvious. *See Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379-80 (Fed. Cir. 2012) (collecting cases). Where present, these object indicia “weigh in favor of nonobviousness, although the lack of such evidence does not weigh in favor of obviousness.” *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870 (Fed. Cir. 1993).

Contrary to Mylan’s contention, there is no “burden-shifting framework” involved in the consideration of nonobviousness in district court litigation. *See In re Cyclobenzaprine*, 676 F.3d at 10777. Objective indicia are “part of the whole obviousness analysis, not just an afterthought.” *Leo Pharm. Prods. Ltd. v. Rea*, 726 F.3d 1346, 1357-58 (Fed. Cir. 2013). They “must be considered in *every case* where present.” *Apple, Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (*en banc*) (emphasis added).

To support nonobviousness, objective indicia must bear a “nexus” to the Asserted Claims, *i.e.*, the indicia must be “attributable to the inventive characteristics of the discovery as claimed in the patent.” *In re Cyclobenzaprine*, 676 F.3d at 1079 n.6. The determination of nexus is “highly fact-dependent and, as such [is] not resolvable by appellate-created categorical rules and

hierarchies as to the relative weight or significance of proffered evidence.” *WBIP*, 829 F.3d at 1331.

Here, the real-world evidence confirms that the Asserted Claims would not have been obvious; rather, the Claims helped fulfill a long-felt clinical need and contributed to Trinza’s commercial success. The evidence also showed that some HCPs—including Mylan’s expert Dr. Berger—were skeptical of the Asserted Claims. Thus, the evidence supports nonobviousness.

- a. The Asserted Claims’ dosing regimens helped Trinza fulfill the long-felt but unmet need for a longer, second-generation LAI

“The existence of a long-felt but unsolved need that is met by the claimed invention is ... objective evidence of non-obviousness.” *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1369 (Fed. Cir. 2017). “It is reasonable to infer that the need would have not persisted had the solution been obvious.” *WBIP*, 829 F.3d at 1332. The need for a “safer, less toxic, and more effective” alternative to existing antipsychotic therapies has been specifically recognized as a basis for finding unmet need. *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006).

LAIAs were developed to address a persistent challenge of treating schizophrenia, patient non-adherence, by reducing dosing frequency. Tr. 871:24-873:23 (Kohler); 1034:24-1035:6, 1060:17-25 (Berger). Longer dosing intervals increase adherence. Tr. 873:13-23 (Kohler).

But LAIAs have their disadvantages. First, longer dosing intervals elevate the risk of sustained and debilitating side effects, including painful muscle contractions and extreme restlessness. Tr. 872:14-24, 875:9-18 (Kohler). Unlike oral medications, which are metabolized in days, LAIAs remain in the body for weeks or months, causing side effects to linger and sometimes requiring additional treatment or hospitalization. Tr. 875:9-24 (Kohler). Thus, though

proper dosing is always important, dosing long-acting drugs is more important because the side effects of overdosing will take longer to abate.

The second disadvantage of LAIAs is that HCPs must administer them. Tr. 874:15-18 (Kohler). Returning for medication frequently can be challenging for patients who must balance their schizophrenia treatment with the rest of their lives. Tr. 874:16-21 (Kohler). As of 2015, there were four second-generation LAIAs on the market in the U.S., with dosing intervals ranging from two weeks to five weeks. Tr. 874:3-10 (Kohler); PTX-089C at 10. Given these relatively short dosing intervals, there “definitely was a need” at that time for an LAIA with a longer dosing interval. Tr. 874:13-15 (Kohler).

Trinza met that need by offering a three-month dosing interval that was more than twice as long as any LAIA on the market at the time. Tr. 876:5-9 (Kohler). Dr. Kohler testified that Trinza was “very well received” by the field and that the medication “frees” patients to pursue a “more independent functioning” lifestyle. Tr. 876:4, 883:24-884:3 (Kohler). Dr. Berger agreed that Trinza is “a wonderful drug.” Tr. 1058:21-24 (Berger).

But it is not Trinza’s long-felt but unmet need that matters here, but the Asserted Claims’ missed dosing regimen. Trinza, for all its benefits, did not eliminate nonadherence. Tr. 884:4-7 (Kohler); 1060:17-19 (Berger) (nonadherence remains a “common occurrence”). And nonadherence to a 3-month LAIA presents unique challenges: undertreatment leading to relapse or overtreatment leading to debilitating side effects further undermining adherence. Tr. 886:4-10 (Kohler). The balance between relapse and side effects is further complicated by clinicians’ “limited knowledge about pharmacokinetics, pharmacodynamics [and] how long the product lasts to exert clinical efficacy.” Tr. 889:15-17 (Kohler).

Enter the Asserted Claims’ missed dosing regimen, which provides “clear instructions about how to catch a person up to the previously effective treatment regimen” without requiring experimentation by practitioners with limited pharmacological knowledge. Tr. 884:8-10, 886:4 (Kohler). Trinza would not have met the long-felt need for a longer-acting LAI without the patented missed dose instructions; clinicians “would have been very reluctant in transferring stable patients on Invega Sustenna to Invega Trinza.” Tr. 889:21-24 (Kohler).

- b. The Asserted Claims’ dosing regimens have contributed to Trinza’s commercial success

“When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention.” *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006). Evidence of commercial success also requires the patentee to establish this nexus between the claimed invention and the commercial success of a product or method. *Datatransury Corp. v. Wells Fargo & Co.*, No. 2:06-CV-072, 2010 U.S. Dist. LEXIS 150694, at \*54 (E.D. Tex. Feb. 26, 2010); *see Alcon Rsch. Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1371 (Fed. Cir. 2012).

The analysis becomes more complex in situations like this one, where there is no question that a product (Trinza) is clearly commercially successful, but the asserted claims are just a portion of the product. *See Ormco.*, 463 F.3d at 1312 (acknowledging that Invisalign clear orthodontic system was commercially successful, but finding that Invisalign’s success was not due to the claimed and novel features, but at least in part to unclaimed features like the aesthetic appeal and improved comfort of transparent devices without brackets and wire). “It is not necessary, however, that the patented invention be solely responsible for the commercial success, in order for this factor to be given weight appropriate to the evidence.” *Cont’l Can Co. v. Monsanto Co.*, 948 F.2d 1264,

1273 (Fed. Cir. 1991). Rather, nexus is established with evidence that “consumers would be less likely to purchase [a product] without” the feature enabled by the patented invention. *Apple*, 839 F.3d at 1054-56 (though many other features contributed to the iPhone’s commercial success and many iPhone owners did not care about it, the slide-to-unlock feature of the iPhone contributed to its commercial success, which was relevant to nonobviousness).

*i. Trinza is a commercial success*

“Invega Trinza’s been a success in the marketplace” by multiple economic metrics. Tr. 1088:17-18 (Mulhern). Trinza has generated more than \$2.5 billion in sales since launch. Tr. 1083:16 (Mulhern); Tr. 1160:10-13 (Stec); PTX-089C at 3; PTX-530. Sales have grown substantially, with an annual compound growth rate of [REDACTED] % since launch, and net sales of \$570 million in 2021. Tr. 1083:13-18 (Mulhern); PTX-089C at 3; PTX-530. Mylan does not dispute the math. Tr. 1160:6-9 (Stec).

This success is despite a crowded LAIA market: nine second-generation LAIAs introduced since the early 2000s. Tr. 1084:19-21 (Mulhern). Nevertheless, Trinza has captured the third-highest share of both treatment days and sales among second-generation LAIAs, representing 8.8% of the total treatment days and 12.6% of 2021 LAIA revenue. Tr. 1086:1-3; 1086:21-24 (Mulhern); PTX-089C; PTX-410; PTX-528. Trinza has generated a larger share of revenue than [REDACTED] [REDACTED] PTX-089C at 48; PTX-410. Among PP LAIAs, Trinza accounted for [REDACTED] % of treatment days for patients eligible to switch from Sustenna in 2021; Janssen is correct that this is particularly notable because Sustenna patients are, by definition, adequately treated and therefore not required to switch to Trinza. Tr. 1088:1-12 (Mulhern); PTX-089C at 25-27, 29-30.

*ii. There is a nexus between the Asserted Claims and Trinza's success*

Janssen readily admits that the missed dose instructions are not the sole driver of Trinza's commercial success, but argues that the Asserted Claims' missed dosing instructions contribute materially to an HCP's decision to prescribe Trinza because the Claims "enable[] the safe and effective treatment in the event of a missed dose of Invega Trinza." Tr. 889:21-24, 892:11-16 (Kohler); 1096:17-20, 1100:2-8, 1101:5-7, 1091:20-21 (Mulhern).

Given the strong potential for missed doses among psychosis patients, clear instructions for resuming treatment following a missed dose are important to any LAIA's safety and long-term efficacy. Tr. 884:8-13 (Kohler). Without such instructions, a clinician would be left to "experiment" on patients with limited knowledge of the drug's PK necessary to determine the best way to resume treatment. Tr. 886:2-10; 890:10-22, 891:23-892:3 (Kohler); PTX-97 at 17. Indeed, a peer-reviewed paper found that the lack of clear directions for re-initiating after a missed dose contributes to clinicians' reluctance to prescribe certain LAIAs in the first instance. PTX-97 at 17.

Janssen's own marketing materials reinforce the nexus. Tr. 1092:6-9; 1094:9-1096:12 (Mulhern); PTX-449 at 1; PTX-509 at 62, 64, 66-68, 76; PTX-510 at 45, 47, 49-51, 58; PTX-513 at 75. Janssen presents the missed dose instructions prominently in its marketing materials and sales training documents, and has even created a "dose illustrator" website to educate clinicians about the pharmacokinetics of Trinza's dosing instructions—including the Claims' missed dose instructions. Tr. 1095:12-1096:3 (Mulhern); PTX-449.

Further supporting the nexus is that a significant number of patients miss LAIA doses. Tr. 884:4-7 (Kohler); 1060:17-25 (Berger) (nonadherence is a "common occurrence ... It is an important challenge."). Thus, HCPs would be very unlikely to switch patients already treated with one PP product (Sustenna) to another using the same active ingredient (Trinza), unless that second

product included clear instructions for how to proceed in the event of a missed dose. Tr. 892:11-23 (Kohler). This further supports that the Asserted Claims “contribute[] to the commercial and clinical acceptability of switching a stable Invega Sustenna patient to Invega Trinza,” Tr. 1091:18-24 (Mulhern), and therefore “contribute to the marketplace success of Invega Trinza,” Tr. 1096:17-20 (Mulhern).

Moreover, the patient population specifically addressed by the Asserted Claims is economically significant. Tr. 1161:1-10 (Stec). Dr. Berger testified that more than 50% of his patients on Trinza miss a regularly schedule dose, and of those, 20 to 30% return more than four months after their prior dose. Tr. 251:5-14 (Berger). Dr. Kohler testified that 5 of the 70 patients he has treated with Trinza, or 7%, have missed a dose and returned in the four-to-nine-month window to resume treatment with Trinza according to the Asserted Claims. Tr. 888:17-21 (Kohler). Both experts’ experiences are consistent with the literature on the frequency of missed doses. Tr. 1092:24-1094:8 (Mulhern) (between 17 and 24% of patients depending on the study).

Moreover, the Court is persuaded by Janssen’s argument that the nexus between Trinza’s commercial success and the Asserted Claims is not limited to sales of doses administered pursuant to the Asserted Claims’ reinitiation dosing regimen. Mylan’s expert, Dr. Stec, acknowledged that a claimed invention need not be the primary driver of commercial success. Tr. 1167:18-19 (“[I]t doesn’t have to be the sole driver[.]”), 1167:23-1168:3 (“Q: If a patent invention contributes but isn’t necessarily the primary driver, is it still relevant? A. It potentially could be, but you do an analysis to determine that.”). Here, the regimen adds significant “option value” like an airbag or other safety feature in a vehicle; though it is not certain, or even probable, that the airbag will ever be needed, it is a significant purchase factor for many buyers. *See* Tr. 1100:12-1101:2 (Mulhern). Thus, the Asserted Claims have contributed to Trinza’s commercial success.

c. Skepticism of the Asserted Claims' efficacy

Evidence of “[d]oubt or disbelief by skilled artisans regarding the likely success of a combination or solution” provides evidence that the solution is nonobvious. *WBIP*, 829 F.3d at 1335. “Concern” that a claimed invention is “risky” is the type of skepticism that “support[s] a conclusion of nonobviousness.” *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377-78 (Fed. Cir. 2019).

Clinicians have expressed skepticism that the Asserted Claims' reinitiation regimen would successfully re-initiate patients on Trinza. Initially, in service of his non-infringement testimony, Dr. Berger testified that it was “unsafe” and “unreasonable” and a “bad idea” to follow the Asserted Claims' regimen. Tr. 262:9-263:9 (Berger). But later, Dr. Berger, recalled to discuss objective indicia as part of Mylan's obviousness case, testified that the Asserted Claims were not unsafe “in all instances.” Tr. 1043:5-10 (Berger). But Dr. Berger then confirmed again that it is “far safer” or “far wiser” to ignore Trinza's FDA-approved label and instead administer the next dose of PP3M to nonadherent patients who return within 4 to 9 months. Tr. 1043:11-24 (Berger).

Dr. Berger also recalled that he and his colleagues doubted whether Trinza would provide the promised therapeutic benefit for the full 3-month dosing interval. Tr. 1058:15-19 (Berger). Dr. Kohler likewise testified that clinicians doubted Trinza's long dosing interval, and that the Asserted Claims' re-initiation regimen could create a “particular challenge,” due to its requirement that patients return to their HCP three times in 35 days. Tr. 885:14-18, 889:13-18 (Kohler). Accordingly, there is ample record in the evidence to support Janssen's contention that the Asserted Claims were met with skepticism.



**C. INVALIDITY: Mylan failed to establish that the Asserted Claims are invalid**

Mylan’s invalidity challenge requires it to prove “by clear and convincing evidence that a person of ordinary skill in the art would not be able to practice the claimed invention without ‘undue experimentation.’” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) (citation omitted). Dr. Forrest opined, in the alternative to his obviousness arguments, that the terms “PP1M” and “PP3M” appearing in the Asserted Claims are: not enabled and lack written description under 35 U.S.C. § 112. In other words, “[i]f the claims aren’t obvious, then [they] are invalid because they lack enablement” and “[t]hose same claims are, if not obvious, invalid because they lack sufficient written description.” Tr. 516:1-8, 750:17-751:2 (Forrest). The Court finds these opinions unpersuasive.

*1. The Asserted Claims are enabled*

“Whether undue experimentation is required is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations [*i.e.*, the *Wands* factors].” *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013) (cleaned up); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The *Wands* factors include:

- (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

*Cephalon*, 707 F.3d at 1336 (quoting *Wands*, 858 F.2d at 737).

The issue with using Dr. Forrest for both obviousness *and* non-enablement/written description is that Dr. Forrest, by virtue of arguing primarily for obviousness (and focusing most

analysis there), lacked “conviction” about the alternative arguments.<sup>31</sup> The arguments are inherently contradictory.

But setting that aside, Mylan argues that a POSA could not practice the full scope of the Asserted Claims without “a lot” of experimentation because (1) the Asserted Claims do not specify the particle size or preferred excipients and concentrations for PP1M and PP3M and the terms are therefore very broad, and (2) there are “no working examples” in the 693 Patent. Tr. 516:21-517:11, 518:3-519:2, 754:6-10 (Forrest). Both are incorrect.

a. The specification provides enough information to practice the Asserted Claims

Although the Asserted Claims do not specify the particle size or excipients (and their concentrations) of PP1M and PP3M, the 693 Patent’s specification *does* disclose those features, and others. Tr. 962:13-963:7 (Little); Tr. 517:23-518:8 (Forrest). Indeed, the 693 Patent contains “ample information in the specification about all the structural features” of PP1M and PP3M such that the specification “hand[s] a person of ordinary skill in the art the recipes to make PP3M and PP1M” for use in the Asserted Claims. Tr. 962:21-963:4 (Little).

First, the 693 Patent contains the concentration and ingredients, specifically PP1M and PP3M “recipes” that contain “sufficient information for a POSA to be able to make and use the claimed invention.” Tr. 963:5-7, 964:14-965:8, 968:24-969:4 (Little); PTX-1 at 13:49-56, 13:62-14:3.<sup>32</sup> Second, The 693 Patent specification also provides the particle size range for PP3M and PP1M, including preferred particle size ranges. PTX-1 at 9:38-01; Tr. 971:5-22 (Little).

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<sup>31</sup> The Court is unpersuaded by Dr. Forrest’s explanation that he did not understand the phrase, “abiding or strong conviction.” Tr. 769:1-20.

<sup>32</sup> PP is the “prodrug” referred to in the specification. A POSA would be familiar with the classes of listed excipients, including wetting agents, suspending agents, and buffers. Tr. 965:12-23 (Little). The 693 Patent specification includes both lists of exemplary excipients and of preferred excipients for PP1M and PP3M. Tr. 965:14-966:20, 967:7-13 (Little); *see, e.g.*, PTX-1 at 10:1-30, 13:3-13; 4:33-39; 13:56-61; 14:9-13.

Third, the 693 Patent specification also provides general and specific manufacturing instructions sufficient to enable a POSA to prepare the particles. PTX-1 at 11:14-29; Tr. 978:13-979:9 (Little). This includes the preferred procedure for adding the surface modifier to the premix, including the concentration of the surface modifier, PTX-1 at 11:50-56; the types of mills that can be used as mechanical means to grind down the particles, PTX-1 at 12:1-6; the preferred grinding media, as well as its density and composition, PTX-1 at 12:24-26; the specific order of steps for adding the premix, PTX-1 at 11:59-61; and the processing temperatures, PTX-1 at 12:34-35. *See* Tr. 979:11-980:19 (Little).

Fourth, the 693 Patent also contains “preferred” examples of the formulations with “specific inactive ingredients” and concentrations, down to the “concentration ... to put into the syringe.” Tr. 967:7-968:1, 969:5-21, 982:21-983:8 (Little); PTX-1 at PTX-1 at 4:33-39, 13:56-62. The 693 Patent also discloses Sustenna as an example of PP1M and Trinza as an example of PP3M. *See* PTX-1 at 4:18-19, 5:23-24, 5:44-46, and 6:63-65 (Sustenna); PTX-1 at 5:42-47 (Trinza). Dr. Forrest is therefore incorrect that there are “no working examples” of PP1M or PP3M.

b. “PP1M” and “PP3M” are not unduly broad

The 693 Patent describes PP1M and PP3M’s structural features. Tr. 962:21-963:4 (Little) (describing structural features as recipes for PP1M and PP3M); Tr. 517:1-6 (Forrest) (“you have to go to the specification to understand what a PP1M and what a PP3M encompasses”); *see also* Tr. 518:3-8, 757:4-8 (Forrest). According to Dr. Forrest, however, the terms PP1M and PP3M encompass “well over 10 million possible combinations” because the structural features include “broad” particle size ranges and “long list[s]” of possible excipients. Tr. 518:3-12, 520:3-14 (Forrest).

However, a POSA would not view the 693 Patent's disclosure about PP1M and PP3M as encompassing 10 million individual formulations. Tr. 980:23-981:6 (Little). It is standard to describe individual formulations using ranges for particle sizes or ingredients. *See* Tr. 1030:23-1031:5 (Little). But even if the Asserted Claims did encompass millions of individual formulations, a POSA would "be able to make any one of those formulations ... without undue experimentation." Tr. 982:8-14 (Little).

First, formulations typically contain inactive ingredients or excipients that help provide the correct dosage form for the active ingredient, which provides the pharmacological effect. Tr. 959:14-960:4 (Little). Wetting agents, buffers, and suspending agents are all classes of excipients included in PP1M and PP3M formulations. Tr. 965:14-23 (Little). Changing or trying different wetting agents is something that a POSA could do without undue experimentation. Tr. 968:5-20 (Little). A POSA would be familiar with the classes of excipients used in PP1M and PP3M, as they are "taught this in their education and they know from their experience what the[ese] class[es] of excipients are and what they do" as well as the "amount that you would use." Tr. 965:14-21, 966:12-20. (Little). Here, the 693 Patent discloses preferred excipients and concentrations. PTX-1 at 14:9-13; 13:56-62; Tr. 967:16-968:1 (Little).

As to particle size, Dr. Forrest could only explain his characterization of the particle size ranges as "broad" based on a six-fold difference in the PP3M range and 20-fold difference for PP1M range. Tr. 519:3-15 (Forrest). But that range is easily explainable: it is "very hard to make particles that are all just one size because [POSAs] start with bigger particles" and "grind them down" resulting in "a range" of particle sizes. Tr. 420:2-12 (Forrest) Tr. 961:7-15 (Little) (opining that it is "very common to refer to particle size as a range."). It is difficult to recreate the exact same particle size distribution between batches, meaning that "it's very important to report them

in terms of a range of particle sizes.” Tr. 972:2-16 (Little). And Dr. Forrest should know: one of his own patents claims particle size ranges with a 10,000-fold difference. Tr. 761:4-8 (Forrest); *see also* Tr. 976:13-16 (Little) [REDACTED]  
[REDACTED] Jindal Dep. Tr.<sup>33</sup>  
42:20-22, 101:20-24, 103:18-104:7.

Dr. Forrest testified repeatedly that the “different particle sizes and all the different excipients” for PP1M and PP3M would require “a lot of different experimentation to test all the possible combinations.” Tr. 517:16-22, 518:9-15, 758:24-759:3. But Dr. Forrest did not proffer evidence that any experimentation is necessary to make and use PP1M and PP3M in the Asserted Claims. To the contrary, a specification “gives a recipe to a person of ordinary skill in the art” such that a POSA would know they “have PP1M” and “have PP3M” by following that recipe without the necessity for experimentation. Tr. 981:19-982:5 (Little). It is undisputed that changes to a formulation can affect its properties, *i.e.*, particle size changes can impact pharmacokinetics. Tr. 848:15-19 (Gobburu); Tr. 1024:18-24 (Little); Tr. 973:1-5 (Little). But there is no evidence that there are any changes here that impede enablement.

Most importantly, Mylan failed to show that *any* particular embodiment of PP3M or PP1M is not enabled. *McRO, Inc. v. Bandai Namco Games Am., Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020) (reversing summary judgment of non-enablement because “[w]ithout any specific examples, the district court’s reasoning is too abstract [and] too conclusory”). Dr. Forrest was unable to identify any specific formulation or explain why it could not be made. Tr. 756:20-757:19, 758:2-9, 758:10-19, 765:15-19, 766:6-13, 766:14-767:6, 767:7-13 (Forrest).

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<sup>33</sup> Mylan Director of R&D Shantanu Jindal.

c. The *Wands* factors support enablement

First, the “amount of direction or guidance presented” and “the presence or absence of working examples” in the 693 Patent support a finding of enablement. *Cephalon*, 707 F.3d at 1336 (quoting *Wands*, 858 F.2d at 737). The “patent’s specification need not ‘describe how to make and use every possible variant of the claimed invention.’” *McRO*, 959 F.3d at 1100 (quoting *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003)). There is likewise “no requirement that a specification must disclose what is routine and well known in the art.” *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Here, the 693 Patent provides guides a POSA to make PP1M and PP3M and use them in the Asserted Claims’ dosing regimen, including a recipe-like disclosure of ingredients, concentrations, and particle size, as well as detailed manufacturing instructions.

Second, to the extent that Mylan asserts that “PP1M” and “PP3M” are too broad, the “scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.” *In re Deuel*, 51 F.3d 1552, 1560 (Fed. Cir. 1995) (quoting *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970)). Here, as discussed above, the Asserted Claims are not unduly broad because they are directed to dosing regimens listing specific formulations, amounts, timing, and injection sites. Nor are “PP1M” or “PP3M” themselves unduly broad, because a POSA would understand the 693 Patent to limit PP1M and PP3M formulations to the specific ingredients, concentrations, and particle sizes (or ranges) in the Patent.

Third, Mylan failed to present any evidence about the quantity of experimentation, which is relevant to determining whether experimentation is undue. *Wands*, 858 F.2d at 737. Even if the terms PP1M and PP3M were understood to encompass tens of thousands of formulations, a POSA would be able to use the 693 Patent’s specifications, including manufacturing instructions, to make

any one of those formulations without undue experimentation. *See also Cephalon*, 707 F.3d at 1339 (“The mere potential need for clinical work, without more, is not dispositive.”); *Ortho-McNeil Pharm., Inc. v. Mylan Lab’ys, Inc.*, 520 F.3d 1358, 1365-66 (Fed. Cir. 2008) (“Even if clinical trials informed the anticonvulsively effective amount, this record does not show that extensive or ‘undue’ tests would be required to practice the invention.”).

And fourth, Dr. Forrest did not testify that the prior art supported *non*-enablement. *Wands*, 858 F.2d at 737. Here his arguments in the alternative simply emphasize the contradiction between testifying, on the one hand, that the prior art makes the Asserted Claims obvious, and on the other, that they are not enabled because they are too vague. Dr. Forrest testified that “a lot was known about [PP]” formulations in the prior art, and that it would have been obvious to make PP1M and PP3M formulations for use in the Asserted Claims’ reinitiation regimen. Tr. 411:23-412:10 (Forrest). Dr. Forrest also testified that the effects of particle size were “well understood.” Tr. 406:19-407:3, 409:11-410:12 (Forrest). This explicitly contradicts any argument that the prior art supported *non*-enablement.

2. *The Asserted Claims do not lack written description*

Mylan also failed to satisfy its burden “to establish by clear and convincing evidence that the written description requirement was not met, in light of the presumption of validity.” *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1364 (Fed. Cir. 2003). The test for written description “is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). This “involves ‘an objective inquiry into the four corners of the specification from the perspective

of a person of ordinary skill in the art.” *Immunex Corp. v. Sandoz, Inc.*, 964 F.3d 1049, 1063 (Fed. Cir. 2020) (quoting *Ariad*, 598 F.3d at 1351).

Here, the entirety of Dr. Forrest’s written description testimony was that there are “no working examples of a PP3M” and “no structural features of a PP1M or a PP3M,” and that the inventors therefore “don’t show they possess the entire claimed range.” Tr. 522:13-20 (Forrest). He added that the 693 Patent incorporates art, such as the 843 Patent that “describes a PP1M that’s five microns that falls right in the range of what they claimed for PP3M.” Tr. 522:20-23 (Forrest).

This can be rejected for the reasons discussed above: the 693 Patent specification provides extensive information about the structural features of PP1M and PP3M including ingredients, concentrations, particle size, manufacturing information, examples of PP1M and PP3M, and commercial embodiments. Based on the specification’s disclosure, it was “very clear that the inventors possessed what was a PP1M formulation and PP3M formulation” within the meaning of the Asserted Claims. Tr. 985:10-24 (Little).

Accordingly, based on this and the other analysis above, the Court finds that Mylan has not sustained its burden of demonstrating obviousness by clear and convincing evidence.


#### **IV. CONCLUSION**

For the reasons above, the Court finds that Janssen has demonstrated by a preponderance of the evidence that Mylan’s Proposed Labels will inevitably induce infringement of the 693 Patent. The Court also finds that Mylan has failed to demonstrate by clear and convincing evidence that the Asserted Claims are invalid. Accordingly, the Court will enter judgment in favor of Janssen and against Mylan as to the 693 Patent. The parties shall submit a joint proposed judgment.



An appropriate Order, which will be filed on the public docket, accompanies this Opinion.

May 15, 2023  
Date

  
\_\_\_\_\_  
Evelyn Padin, U.S.D.J.



US010143693B2

(12) **United States Patent**  
**Gopal et al.**

(10) **Patent No.:** **US 10,143,693 B2**

(45) **Date of Patent:** **Dec. 4, 2018**

(54) **DOSING REGIMEN FOR MISSED DOSES  
FOR LONG-ACTING INJECTABLE  
PALIPERIDONE ESTERS**

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Nieuwstraat (BE); **Mahesh Narain  
Samtani**, Flemington, NJ (US)

(73) Assignee: **Janssen Pharmaceuticals, Inc.**, Beerse  
(BE)

(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/090,889**

(22) Filed: **Apr. 5, 2016**

(65) **Prior Publication Data**

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**Related U.S. Application Data**

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15, 2015, provisional application No. 62/144,054,  
filed on Apr. 7, 2015.

(51) **Int. Cl.**  
**A61K 31/519** (2006.01)  
**A61K 9/00** (2006.01)  
**A61K 9/14** (2006.01)

(52) **U.S. Cl.**  
CPC ..... **A61K 31/519** (2013.01); **A61K 9/0019**  
(2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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*Primary Examiner*—Bong-Sook Baek

(57) **ABSTRACT**

The present application provides a method for treating  
patients in need of psychiatric treatment, wherein said  
patient is being treated with the 3-month formulation of  
paliperidone palmitate and fails to take the next scheduled  
dose of the 3-month formulation of paliperidone palmitate.

**29 Claims, 7 Drawing Sheets**

Defendant's Exhibit

**DTX-001**

3 20-cv-13103

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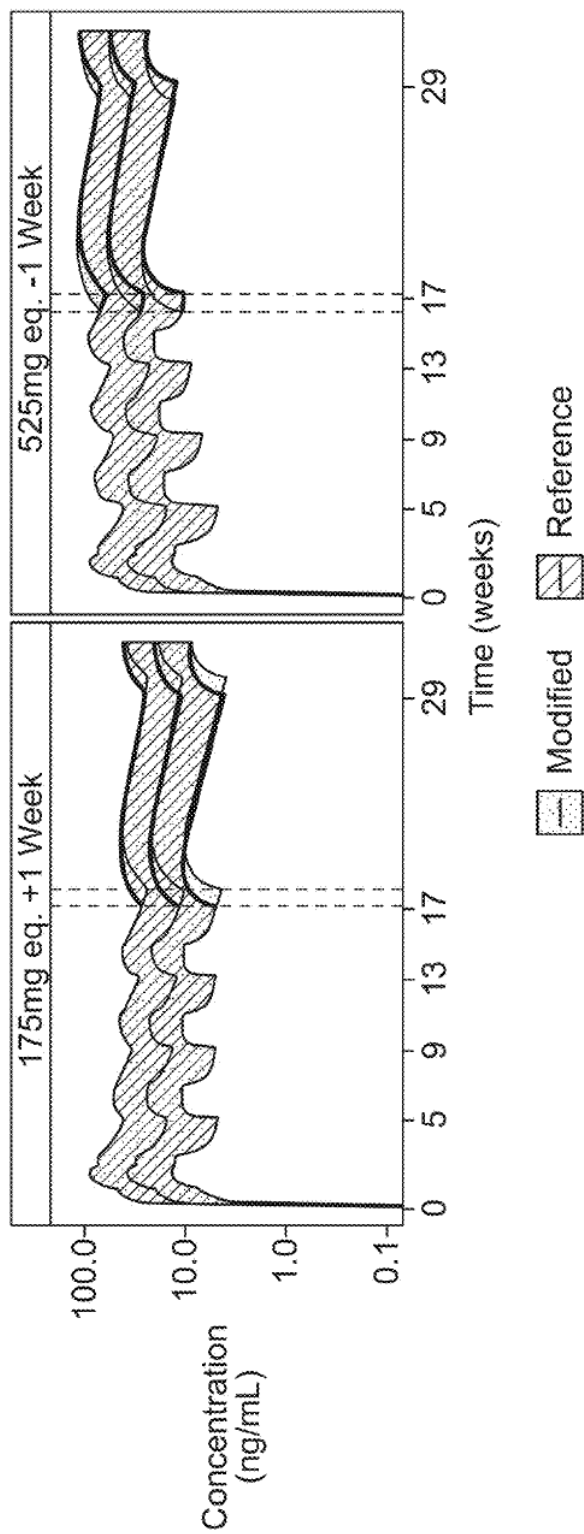
U.S. Patent

Dec. 4, 2018

Sheet 1 of 7

US 10,143,693 B2

**FIG. 1**



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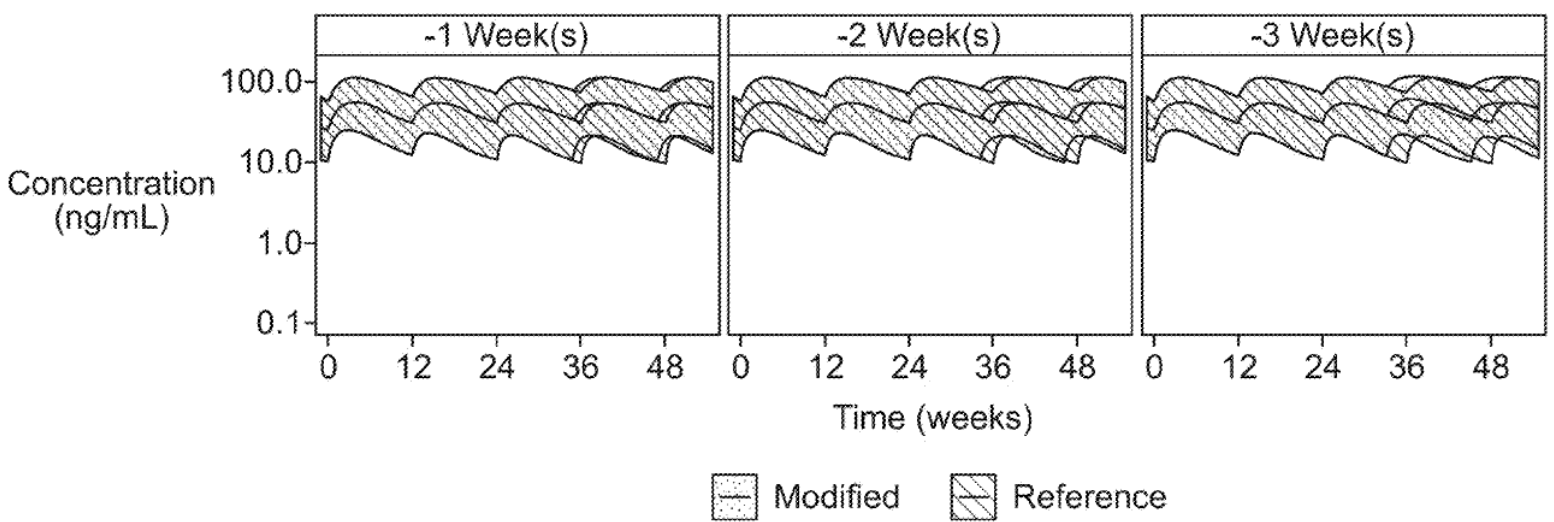
U.S. Patent

Dec. 4, 2018

Sheet 2 of 7

US 10,143,693 B2

**FIG. 2A**



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Appx00080

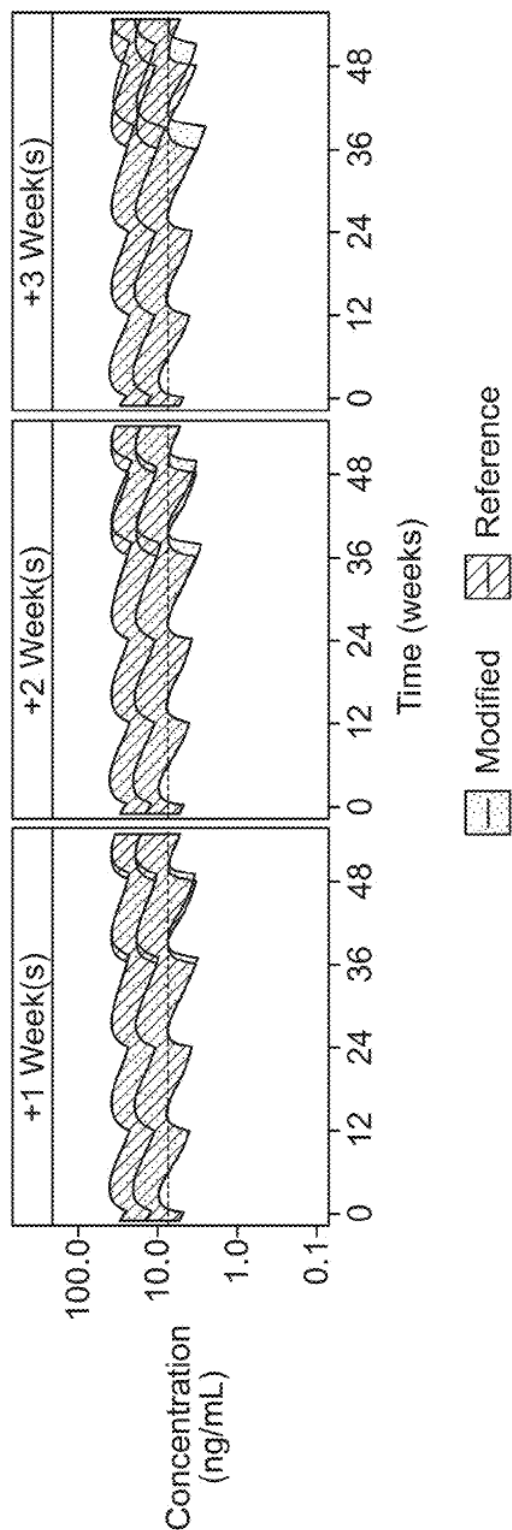
U.S. Patent

Dec. 4, 2018

Sheet 3 of 7

US 10,143,693 B2

**FIG. 2B**



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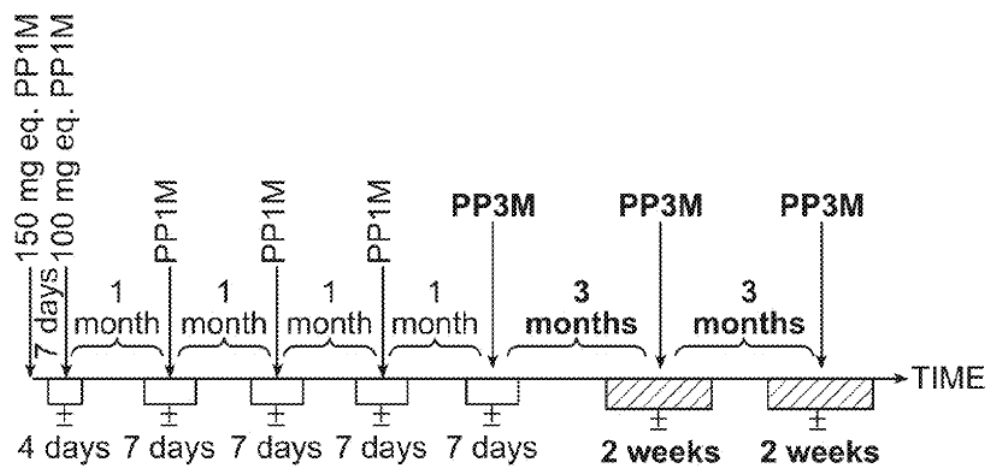
U.S. Patent

Dec. 4, 2018

Sheet 4 of 7

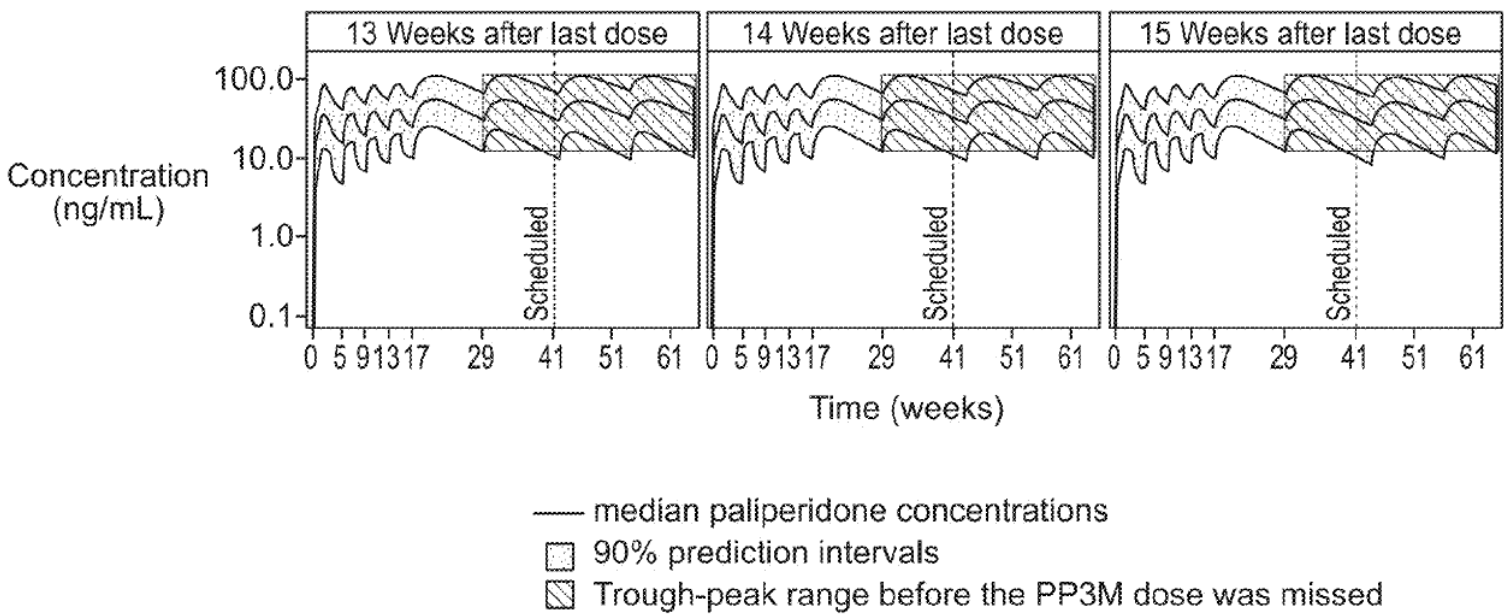
US 10,143,693 B2

**FIG. 3**



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**FIG. 4A**



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Appx00083

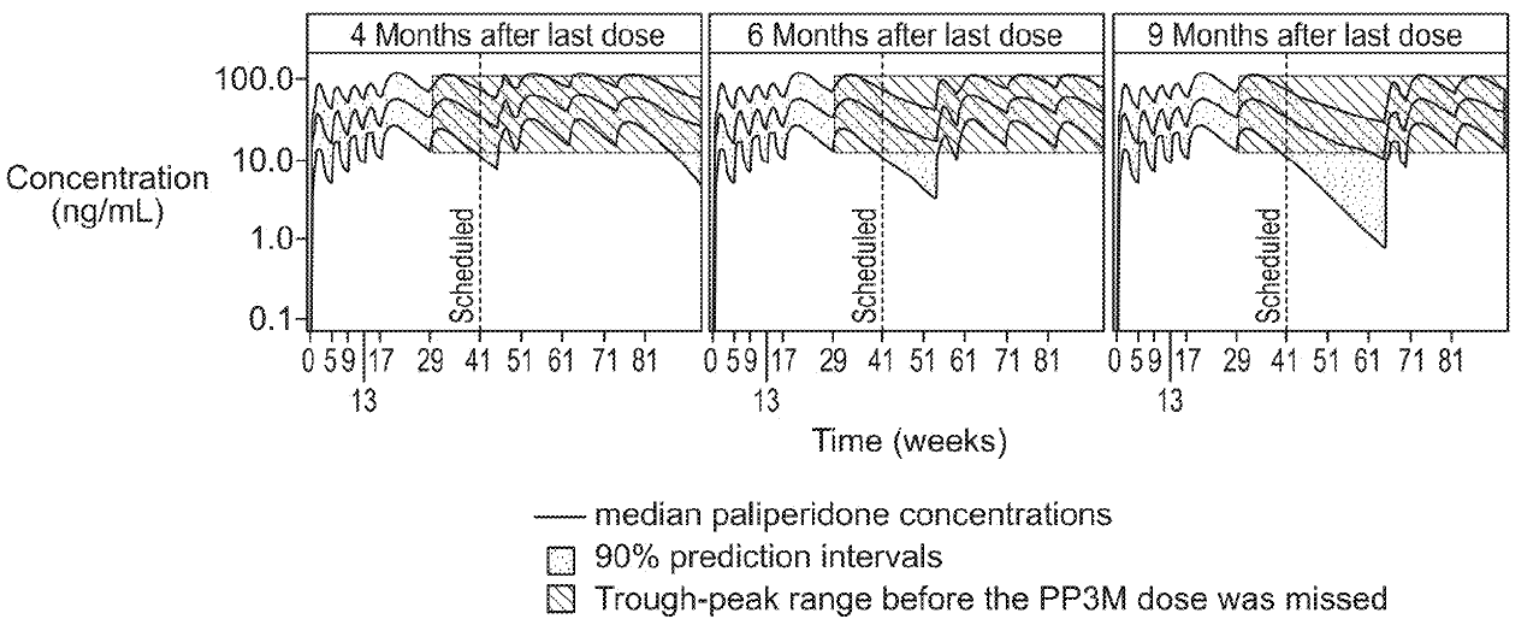
U.S. Patent

Dec. 4, 2018

Sheet 6 of 7

US 10,143,693 B2

**FIG. 4B**



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Appx000084



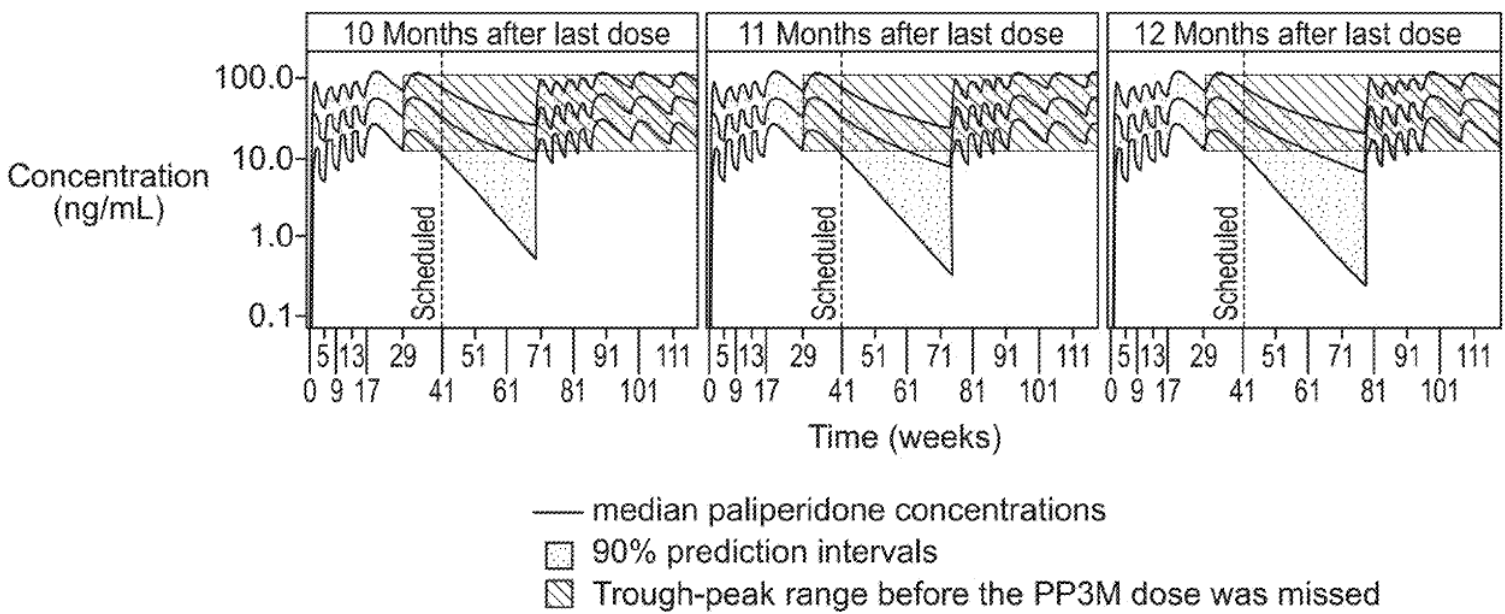
U.S. Patent

Dec. 4, 2018

Sheet 7 of 7

US 10,143,693 B2

**FIG. 4C**



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Appx00085

US 10,143,693 B2

1

## DOSING REGIMEN FOR MISSED DOSES FOR LONG-ACTING INJECTABLE PALIPERIDONE ESTERS

### CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Application No. 62/144,054, filed on Apr. 7, 2015 and Application No. 62/162,596, filed on May 15, 2015, each of which is incorporated herein by reference

### FIELD OF THE INVENTION

This invention relates to a method for treating patients who have missed a treatment of 3-month paliperidone palmitate extended-release injectable suspension formulation.

### BACKGROUND OF THE INVENTION

Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Antipsychotics were first introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D<sub>2</sub> and serotonin (5-hydroxytryptamine type 2A) antagonism of the second generation, atypical antipsychotic drugs. Paliperidone (9-OH risperidone) is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

3-monthly Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other related diseases that are normally treated with antipsychotic medications. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

Many patients with the mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. adherence problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies. Once monthly Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone, which may greatly enhance compliance with dosing. Paliperidone palmitate formulated as an aqueous nanosuspension is described in U.S. Pat. Nos. 6,077,843 and 6,555,544. In addition, a dosing regimen of paliperidone palmitate for treating patients is disclosed in US Patent Application Publication No. 20090163519.

2

Paliperidone palmitate is an atypical antipsychotic drug administered by injection. The original formulation of paliperidone palmitate was a once-monthly antipsychotic and was approved for the treatment of schizophrenia in adults in numerous countries. The acute and sustained efficacy and tolerability profile of once-monthly paliperidone palmitate has been demonstrated in clinical studies totalling more than 3800 patients. Continued treatment with once-monthly paliperidone palmitate in patients who initially responded to it for acute worsening of symptoms resulted in a nearly 4-fold reduction in relapse risk compared with patients randomized to placebo. A recently developed 3-month formulation offers a substantially longer dosing interval: injections are administered once every 3 months. This extended dosing interval offers the prospect of fewer opportunities for nonadherence than currently available long acting injectable formulations, thus reducing relapse risk as a result of subtherapeutic plasma concentration and its associated negative consequences in patients with schizophrenia.

Even with a drug administered once every 3 months or every 12 weeks ( $\pm 3$  weeks) or 13 weeks  $\pm 2$ , patients at time miss their doses of medication. Consequently, there is a need to reinstitute a dosing regimen for patients who miss their regularly scheduled dose of medication. Thus, the objective of the present application is to provide a dosing regimen of paliperidone palmitate for patients in need of a treatment who have missed their 3 month ( $\pm 2$  weeks) dose of paliperidone palmitate 3-month extended-release injectable suspension.

### SUMMARY OF THE INVENTION

In one embodiment of the present invention there is provided a dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with a 3-month injectable paliperidone palmitate depot, wherein said patient misses for a period of between about four months and about nine months (inclusive e.g. four months or more but nine months or less) the next scheduled maintenance dose of the 3-month injectable paliperidone palmitate depot, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of the monthly injectable paliperidone palmitate depot on day one;
- (2) administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation dose of the monthly injectable paliperidone palmitate depot on about the 8<sup>th</sup> day  $\pm 4$  (e.g. 4th day to about the 12th day) after administering of said first reinitiation loading dose; and

Missed PP3M dose	Administer PP1M, two doses (into deltoid muscle)		(into deltoid <sup>a</sup> or gluteal muscle) Maintenance Dose
	First Reinitiation Dose	Second Reinitiation Dose	
175 mg eq.	50 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	100 mg eq.	525 mg eq.

- (3) administer intramuscularly in the deltoid or gluteal muscle of said patient the 3-month formulation of

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US 10,143,693 B2

3

paliperidone palmitate in the range of about 175 mg eq. to about 525 mg eq. on about the 30th day $\pm$ 7 (e.g. 23rd day to about the 37th day) after administering of the second reinitiation dose of monthly injectable paliperidone palmitate.

In another embodiment of the present invention there is provided a dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with a 3-month injectable paliperidone palmitate depot, wherein said patient misses for a period of more than nine months the next scheduled maintenance dose of the 3-month injectable paliperidone palmitate depot, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of 150 mg eq. of the monthly injectable paliperidone palmitate depot;
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of 100 mg eq. the monthly injectable paliperidone palmitate depot on about the 4th day to about the 12th day after administering of said first reinitiation loading dose;
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a first reinitiation maintenance dose of 50 mg eq. to about 150 mg eq. of the monthly injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of said second reinitiation loading dose;
- (4) administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of monthly injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of the first maintenance additional dose;
- (5) administering intramuscularly in the deltoid or gluteal muscle of said patient a third reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of monthly injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of the second maintenance dose; and
- (6) administering intramuscularly in the deltoid or gluteal muscle of said patient from about 175 mg eq. to about 525 mg eq. of the 3-month formulation of paliperidone palmitate on about the 23rd day to about the 37th day after administering of the third maintenance dose of monthly injectable paliperidone palmitate.

Additional maintenance doses may be administered before the readministration of the 3-month formulation of paliperidone palmitate (e.g. a fourth maintenance dose, fifth maintenance dose).

This and other objects and advantages of the present invention may be appreciated from a review of the present application.

#### DETAILED DESCRIPTION OF FIGURES

FIG. 1 illustrates the switching from PP1M to PP3M at default week 17 $\pm$ 1 Week.

FIGS. 2A-2B illustrate the dosing windows around the regularly scheduled 12-week dosing interval. Graphs of modeled results of dosing before regularly scheduled injections of (A) 525 mg eq. PP3M (B) 175 mg eq. PP3M.

FIG. 3 illustrates the dosing windows for PP1M and PP3M dosing regimen.

4

FIGS. 4A-4C illustrate predicted plasma concentration of PP3M (525 mg eq.). Graphs of modeled results of missed dosing for (A) <4 months. (B) between 4 to 9 months (C) >9 months.

#### DETAILED DESCRIPTION

3-month paliperidone palmitate extended-release injectable suspension is an antipsychotic medication which is the ester of the active ingredient paliperidone. Paliperidone is effective for the treatment of psychosis and has been used to treat schizophrenia and schizoaffective disorders. The 3-month paliperidone palmitate extended-release injectable suspension suitable for the treatment of psychotic disorders including but not limited to schizophrenia and/or schizoaffective disorders. It is recommended that the 3-month paliperidone palmitate extended-release injectable suspension be administered to patients who have been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension (e.g. INVEGA SUSTENNA®) for a several months and it is recommended for at least four months.

3-month paliperidone palmitate extended-release injectable suspension preferably will be provided with an adequate dose of paliperidone palmitate generally in the range of about 250 mg to about 900 mg of paliperidone palmitate to provide a sustained therapeutic concentration of paliperidone over the three month dosing interval to the patient. Preferably the aqueous extended-release suspension for intramuscular injection will be provided in dose strengths of about 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 175 mg eq., 263 mg eq., 350 mg eq., and 525 mg eq. of paliperidone, respectively. 3-month paliperidone palmitate extended-release injectable suspension is preferably provided in a prefilled syringe (cyclic-olefin-copolymer) prefilled with either 175 mg eq. (0.875 mL), 263 mg eq. (1.315 mL), 350 mg eq. (1.75 mL), or 525 mg eq. (2.625 mL) paliperidone (as 273 mg, 410 mg, 546 mg, or 819 mg paliperidone palmitate) suspension with a plunger stopper and tip cap (bromobutyl rubber), a backstop, and 2 types of commercially available needles: a thin walled 22G, 1½-inch safety needle and a thin walled 22G, 1-inch safety needle.

3-month paliperidone palmitate extended-release injectable suspension is intended for intramuscular use only. It is not recommended not to administer by any other route. Care should be taken to avoid inadvertent injection into a blood vessel. Dose should be administered in a single injection; it should not be administered in divided injections as this would change the release profile and has not been studied in clinical trials. It is preferred that injections be administered slowly, deep into the deltoid or gluteal muscle. 3-month paliperidone palmitate extended-release injectable suspension is preferred to be administered using only the thin wall needles to reduce the risk of blockage.

#### Deltoid Injection

Currently the recommended needle size for administration of 3-month paliperidone palmitate extended-release injectable suspension into the deltoid muscle is determined by the patient's weight:

For patients weighing less than 90 kg, the 1-inch, 22 gauge thin wall needle is recommended.

For patients weighing 90 kg or more, the 1½-inch, 22 gauge thin wall needle is recommended.

It is currently preferred that 3-month paliperidone palmitate extended-release injectable suspension be administered into the center of the deltoid muscle. It is also preferred that deltoid injections should be alternated between the two deltoid muscles.

EXPERTS\_MYL\_002383



US 10,143,693 B2

5

**Gluteal Injection**

Currently, the preferred needle size for administration of 3-month paliperidone palmitate extended-release injectable suspension into the gluteal muscle is the 1½-inch, 22 gauge thin wall needle regardless of patient weight. It is preferred that 3-month paliperidone palmitate extended-release injectable suspension be administered into the upper-outer quadrant of the gluteal muscle. It is also preferred that gluteal injections should be alternated between the two gluteal muscles.

**Incomplete Administration**

To avoid an incomplete administration of 3-month paliperidone palmitate extended-release injectable suspension, it is recommended that to ensure that doses are completely administered that the syringes be vigorously shaken and/or mechanical agitated to obtain a uniform dispersion of the suspension, preferably the suspension will be shaken vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension and ensure the needle does not get clogged during injection.

It is preferred that 3-month paliperidone palmitate extended-release injectable suspension is to be used only after the 1-month paliperidone palmitate extended-release injectable suspension (e.g. INVEGA SUSTENNA®) has been established as adequate treatment for at least four months. In order to establish a consistent maintenance dose, it is preferred that at least the last two doses of 1-month paliperidone palmitate extended-release injectable suspension be the same dosage strength before starting 3-month paliperidone palmitate extended-release injectable suspension.

The preferred time to initiate dosing a patient with 3-month paliperidone palmitate extended-release injectable suspension is when the next 1-month paliperidone palmitate dose was to be scheduled with a 3-month paliperidone palmitate extended-release injectable suspension dose based on the previous 1-month injection dose as shown in Table 1. 3-month paliperidone palmitate extended-release injectable suspension may be administered up to about 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.

TABLE 1

Conversion From the Last 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension (INVEGA SUSTENNA®) Dose To the 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension (INVEGA TRINZA™) Dose Using 3.5 as a Multiplier	
If the last 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension dose is about:	Initiate 3-month paliperidone palmitate extended-release injectable suspension at about the following dose:
50 mg eq.	175 mg eq.
75 mg eq.	263 mg eq.
100 mg eq.	350 mg eq.
150 mg eq.	525 mg eq.

Conversion from the 39 mg 1-month paliperidone palmitate extended-release injectable suspension was not studied.

Following the initial 3-month paliperidone palmitate extended-release injectable suspension, 3-month paliperidone palmitate extended-release injectable suspension

6

should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 273 mg to 819 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of 3-month paliperidone palmitate extended-release injectable suspension, the patient's response to an adjusted dose may not be apparent for several months.

**Missed Doses****Dosing Window**

Missing doses of 3-month paliperidone palmitate extended-release injectable suspension should be avoided. However, on exceptional occasions, patients may be given the injection up to about 2 weeks before or after the 3-month time point.

**Missed Dose >3½ Months and <4 Months Since Last Injection**

If more than 3½ months (up to but less than 4 months) have elapsed since the last injection of 3-month paliperidone palmitate extended-release injectable suspension, the previously administered 3-month paliperidone palmitate extended-release injectable suspension dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

**Missed Dose Greater than or Equal to 4 Months Up to 9 Months Since Last Injection**

If between 4 to 9 months have elapsed since the last injection of 3-month paliperidone palmitate extended-release injectable suspension, do NOT administer the next dose of 3-month paliperidone palmitate extended-release injectable suspension. Instead, use the re-initiation regimen shown in Table 2.

TABLE 2

Re-Initiation Regimen After Missing ≥4 months up to 9 Months of 3-Month Extended-Release Injectable Suspension Dose			
Last 3-Month Extended Release Injectable Suspension	Administer PP1M, two doses one week apart (into deltoid muscle)		Then administer 3-Month Extended Release Injectable Suspension Dose (into deltoid* or gluteal muscle)
dose	Day 1	Day 8	1 month after day 8
175 mg eq.	50 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	100 mg eq.	525 mg eq.

\*See Instructions for Use for deltoid injection needle selection based on body weight.

**Missed Dose >9 Months Since Last Injection**

If more than 9 months have elapsed since the last injection of 3-month paliperidone palmitate extended-release injectable suspension, re-initiate treatment with the 1-month paliperidone palmitate extended-release injectable suspension as described in the prescribing information for that product. 3-month paliperidone palmitate extended-release injectable suspension can then be resumed after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least 4 months.

**1-Month Paliperidone Palmitate Extended-Release Injectable Suspension Dosing**  
The published US drug label for INVEGA SUSTENNA® 1-month paliperidone palmitate extended-release injectable suspension provides the appropriate dosing instructions for such product at various doses. This dosing regimen is also generally described in U.S. Patent Application No.

EXPERTS\_MYL\_002384

7

The models or simulations also indicate that 1-month paliperidone palmitate extended-release injectable suspension may be administered by intramuscular injection into either deltoid or gluteal muscle. The first and second loading dose of the initiation regimen may be administered in the deltoid muscle and the maintenance dose of the maintenance regimen may be administered in either the deltoid or gluteal muscle. The injection into the deltoid muscle may be delivered by a 1-inch 23-Gauge (G) or 1.5-inch 22-G needle based on the patient's weight. For the patients whose body weights are less than about 90 kg or 200 lb, a 1-inch 23-G needle may be used for administration, and for those body weights are equal or more than about 90 kg or 200 lb, a 1.5-inch 22-G needle may be used for administration. The injection into the gluteal muscle may be delivered by a 1.5-inch 22-G needle for all body weights.

8

Also used herein, the terms "the first loading dose of the reinitiation regimen", "the first dose of the reinitiation regimen", "the first reinitiation dose" or variant thereof refer to the dose to be administered on day 1 when patients return to treatment. Similarly, the terms "the second loading dose of the reinitiation regimen", "the second dose of the reinitiation regimen", "the second reinitiation dose" or variant thereof refer to the dose to be administered on day 2 when patients return to treatment.

**Appx00089**



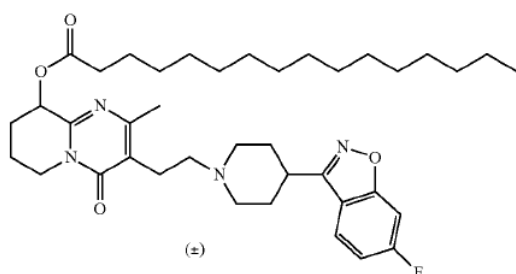
US 10,143,693 B2

9

tiation regimen", "the second reinitiation dose" or variant thereof refer to the dose to be administered after a week after the treatment day 1; and the terms "the maintenance dose of the reinitiation regimen", "the reinitiation maintenance dose" or variant thereof refer to the dose to be administered monthly after the treatment day 8.

#### Extended-Release Injectable Suspension Formulations

Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, which contains a racemic mixture of (+)- and (-)-paliperidone, which are described in U.S. Pat. No. 5,254,556 (incorporated herein by reference). The chemical name for paliperidone palmitate is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-c]pyrimidin-9-yl hexadecanoate. The structural formula is:



Paliperidone esters may be formulated with pharmaceutical excipients into injectable dosage forms as described in U.S. Pat. Nos. 5,254,556 and 6,077,843 both of which are incorporated herein by reference. Injectable formulations may be formulated in aqueous carriers.

Suitable aqueous depot formulations are described in U.S. Pat. No. 6,077,843 which is incorporated herein by reference. The 3-month formulations would have an average size of less than about 20  $\mu\text{m}$  to about 3  $\mu\text{m}$ . Preferably the particles would have an average particle size (d50) of from about 10  $\mu\text{m}$  to about 3  $\mu\text{m}$ ; preferably about 9  $\mu\text{m}$  to about 4  $\mu\text{m}$ .

The 1-month aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would be of an average size of less than about 2,000 nm to about 100 nm. Preferably the nano particles would have an average particle size (d50) of from about 1,600 nm to about 400 nm and most preferably about 1,400 nm to about 900 nm. Preferably the d90 will be less than about 5,000 nm and more preferably less than about 4,400 nm.

As used herein, an effective average particle size (d50) of less than about 2,000 nm means that at least 50% of the particles have a diameter of less than about 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least about 90%, e.g. about 5,000 nm. Most preferably, about 90% of the particles have a size of less than about 4,400 nm.

Suitable aqueous nanoparticle depot 1-month formulations are described in U.S. Pat. No. 6,555,544 which is incorporated herein by reference. In one embodiment of the present invention the formulation would comprise nanoparticles, a surfactant, a suspending agent, and optionally one or more additional ingredients selected from the group consisting of preservatives, buffers and an isotonicizing agent.

10

Useful surface modifiers paliperidone palmitate formulations are believed to include those that physically adhere to the surface of the active agent but do not chemically bond thereto. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available TWEEN<sup>SM</sup>, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecyl sulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminate silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as PLURONIC<sup>SM</sup> F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as TETRONIC<sup>SM</sup> 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT<sup>SM</sup> (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; DUPO-NOL<sup>SM</sup> P which is a sodium lauryl sulfate available from DuPont; TRITON<sup>SM</sup> X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; TWEEN<sup>SM</sup> 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Speciality Chemicals; SPAN<sup>SM</sup> 20, 40, 60 and 80 which are sorbitan esters of fatty acids; ARLACEL<sup>SM</sup> 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; CARBOWAX<sup>SM</sup> 3550 and 934 which are polyethylene glycols available from Union Carbide; CRODESTA<sup>SM</sup> F110 which is a mixture of sucrose stearate and sucrose distearate available from Croda Inc.; CRODESTA<sup>SM</sup> SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is  $\text{C}_{18}\text{H}_{17}\text{CH}_2(\text{CON}(\text{CH}_3)\text{CH}_2(\text{CHOH})_4\text{CH}_2\text{OH})_2$ . The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic<sup>SM</sup> F108 and Pluronic<sup>SM</sup> F68.

Pluronic<sup>SM</sup> F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula  $\text{HO}[\text{CH}_2\text{CH}_2\text{O}]_x[\text{CH}(\text{CH}_3)\text{CH}_2\text{O}]_y[\text{CH}_2\text{CH}_2\text{O}]_z\text{H}$  in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag NONIONIC<sup>SM</sup> 1108-F available from Hodag, and SYNPERONIC<sup>SM</sup> PE/F108 available from ICI Americas.

EXPERTS\_MYL\_002386

US 10,143,693 B2

11

The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the antipsychotic agent, etc. The specific surface modifier preferably is present in an amount of about 0.1 to about 1 mg per square meter surface area of the paliperidone palmitate. It is preferred in the case of paliperidone palmitate (9-hydroxyrisperidone palmitate) to use PLURONIC™ F108 as a surface modifier, a relative amount (w/w) of both ingredients of approximately 6:1 is preferred.

The particles of this invention can be prepared by a method comprising the steps of dispersing paliperidone palmitate in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the antipsychotic agent to an effective average particle size. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles for the 1-month formulation described herein includes (a) obtaining paliperidone palmitate in micronized form; (b) adding the micronized paliperidone palmitate to a liquid medium to form a premix; and (c) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the effective average particle size.

The paliperidone palmitate in micronized form may be prepared using techniques known in the art. It is preferred that the particle size of the micronized paliperidone palmitate be less than about 100  $\mu\text{m}$  as determined by sieve analysis. If the particle size of the micronized paliperidone palmitate is greater than about 100  $\mu\text{m}$ , then it is preferred that the particles of paliperidone palmitate be reduced in size to less than 100  $\mu\text{m}$ .

The micronized paliperidone palmitate can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of paliperidone palmitate in the liquid medium (weight by weight percentage) can vary widely and depends on the selected antipsychotic agent, the selected surface modifier and other factors. Suitable concentrations of paliperidone palmitate in compositions vary from about 0.1% to about 60%, preferably is from about 0.5% to about 30%, and more preferably, is approximately 7% (w/v). It is currently preferred to use a concentration of about 100 mg eq of paliperidone per ml or about 156 mg of paliperidone palmitate per ml.

A more preferred procedure involves the addition of a surface modifier to the premix prior to its subjection to mechanical means to reduce the effective average particle size. The concentration of the surface modifier (weight by weight percentage) can vary from about 0.1% to about 90%, preferably from about 0.5% to about 80%, and more preferably is approximately 7% (w/v).

The premix can be used directly by subjecting it to mechanical means to reduce the effective average particle size in the dispersion to less than about 2,000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the antipsychotic agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation such as, for example, a roller mill or a Cowles type mixer, until a homogeneous dispersion is achieved.

The mechanical means applied to reduce the effective average particle size of the antipsychotic conveniently can

12

take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills—such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is anywhere between about 0.1 Pa·s and about 1 Pa·s. For ball milling, the apparent viscosity of the premix preferably is anywhere between about 1 mPa·s and about 100 mPa·s.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, about 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles which are acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and about 95% ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than about 2.5 g/cm<sup>3</sup> and include about 95% ZrO stabilized with magnesia and polymeric beads.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For rolling mills, processing times of up to two days or longer may be required for smaller size particles.

The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than about 30° C. to about 40° C. are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed by, for example, shaking vigorously. Optionally, the dispersion can be subjected to a sonication step using, for example, an ultrasonic power supply.

Aqueous compositions according to the present invention conveniently further comprise a suspending agent and a buffer, and optionally one or more of a preservative and an isotonicizing agent. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonicizing agent.

Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxypropylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of about 0.5 to about 2%, most preferably about 1% (w/v).

Suitable wetting agents preferred from the listed surfactant for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a con-

EXPERTS\_MYL\_002387



US 10,143,693 B2

13

centration of about 0.5% to about 3%, more preferably about 0.5% to about 2%, most preferably about 1.1% (w/v).

Suitable buffering agents are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to the pH value of about 8.5), preferably in the pH range of about 7 to about 7.5. Particularly preferred is the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9% (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6% (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein.

Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic acid, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-gamma-piccolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to about 2% (w/v), preferably up to about 1.5% (w/v).

Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from about 0% to about 10% (w/v) isotonizing agent. Mannitol may be used in a concentration from about 0% to about 7% more preferably, however, from about 1% to about 3% (w/v), especially from about 1.5% to about 2% (w/v) of one or more electrolytes are used to render the suspension isotonic, apparently because ions help to prevent flocculation of the suspended ester. In particular, electrolytes of the buffer serve as isotonizing agent.

A particularly desirable feature for an injectable depot formulation relates to the ease with which it can be administered. In particular such an injection should be feasible using a needle as fine as possible in a span of time which is as short as possible. This can be accomplished with the aqueous suspensions of the present invention by keeping the viscosity below about 75 mPa-s, preferably below about 60 mPa-s. Aqueous suspensions of such viscosity or lower can both easily be taken up in a syringe (e.g. from a vial), and injected through a fine needle (e.g. a 21G 1½ inch, 22G 2 inch, 22G 1¼ inch or 23G 1 inch needle). The preferred needles for injection are 22G 22G 1½ inch regular wall and 23G 1 inch regular wall needles.

Ideally, aqueous suspensions according to the present invention will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular for the 3-month formulation the composition will be (a) from about 280 to about 350 mg/mL of prodrug; (b) from about 8 to about 12 mg/mL of wetting agent; (c) from about 16 to about 22 mg/mL of one or more buffering agents to render the neutral to very slightly basic (pH 8.5); (d) from about 65 to about 85 mg/mL of a suspending agent; (e) up to about 2% (w/v) preservatives; and (f) water q.s. ad 100%. Most preferably the inactive ingredients in the 3-month formulation will be polysorbate 20 (about 10 mg/mL), polyethylene glycol 4000 (about 75 mg/mL), citric acid monohydrate (about 7.5 mg/mL), sodium dihydrogen phosphate monohydrate (about 6 mg/mL), sodium hydroxide (about 5.4 mg/mL) and water for injection. In particular, such a composition for the 1-month formulation will comprise by weight based on the total volume of the composition: (a) from about 3% to 20% (w/v) of the prodrug; (b) from about 0.5% to 2% (w/v) of a wetting agent; (c) one or more buffering agents sufficient to render the composition neutral

14

to very slightly basic (pH 8.5); (d) from about 0.5% to about 2% (w/v) of a suspending agent; (e) up to about 2% (w/v) preservatives; and (f) water q.s. ad 100%. Preferably the aqueous suspension will be made under sterile conditions and no preservatives will be used. Appropriate methods to aseptically prepare paliperidone palmitate are described in WO 2006/114384 which is hereby incorporated by reference herein.

The preferred aqueous dosage form contains inactive ingredients that are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection.

As used herein, a dose or dosing is expressed as milligrams (mg) of paliperidone palmitate. Paliperidone palmitate dosing may also be expressed as mg equivalents (mg eq.) of paliperidone with about 39, 78, 117, 156, and 234 mg of paliperidone palmitate being equivalent to about 25, 50, 75, 100 and 150 mg eq., of paliperidone, respectively. For three month depot dosing it is preferred to dose patients with about 175 mg eq. to about 525 mg eq. paliperidone or about 273 mg to about 819 mg paliperidone palmitate.

The term "antipsychotics" or "antipsychotic drug medication" as used herein means any medication used to decrease or ameliorate the symptoms of psychosis in a person with a psychotic disorder.

The term "psychiatric patient" as used herein, refers to a human, who has been the object of treatment, or experiment for a "mental disorder" and "mental illness" refer to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone esters (e.g. paliperidone palmitate) can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evidenced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform disorders, in DSM-IV-TR such as category 295.xx. Bipolar Disorder refers to a condition characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be associated with psychotic features include, but are not limited to the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress. Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Pre-

EXPERTS\_MYL\_002388



US 10,143,693 B2

15

dominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusions (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium

16

(292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83). The numbers in parenthesis refer to the DSM-IV-TR categories.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. By way of example, an effective amount of paliperidone for the treatment of mental disorders would be from about 0.01 mg/kg to about 2 mg/kg body weight per day. For monthly depot dosing it is preferred to dose patients with about 25 mg-eq. to about 150 mg eq. paliperidone or about 39 mg to about 234 mg paliperidone palmitate. The amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g. 156 mg corresponds to paliperidone 100 mg). For three month depot dosing it is

EXPERTS\_MYL\_002389

US 10,143,693 B2

17

preferred to dose patients with about 175 mg eq. to about 525 mg eq. paliperidone or about 273 mg to about 819 mg paliperidone palmitate.

TABLE 3

Conversion between mg PP and mg eq. paliperidone for PP1M and PP3M

PP1M Dose (mg PP)	PP1M Dose (mg eq. Paliperidone)	PP3M Dose (mg PP)	PP3M Dose (mg eq. Paliperidone)
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

PP, paliperidone palmitate;  
PP3M, PP 3-month formulation;  
PP1M, PP 1-month formulation.

The following non-limiting examples are provided to further illustrate the present invention.

## Example 1. Methodology

## Population Pharmacokinetics Models

A comprehensive population pharmacokinetics (PK) model was developed for paliperidone palmitate based on data from previous studies of subjects with schizophrenia. Briefly, a population PK model was developed, using the first-order conditional estimation method (FOCE), to estimate the population PK parameters of paliperidone after single and multiple dose administration of PP3M. The population PK model was constructed using data from a phase-I (NCT01559272) and phase-III study (NCT01529515). The final population PK model was based on 8990 PK samples from 651 patients.

The PP1M and PP3M models were one-compartment models with first-order elimination. In the PP1M absorption sub-model, a fraction of the dose entered the central compartment relatively quickly via a zero-order process. After a certain lag time, the remaining fraction of the dose entered the systemic circulation via a first-order process. The PP3M absorption sub-model consisted of 2 saturable absorption processes.

## Model Based Simulations

The population PK model was used for simulating pre-defined dosing regimen scenarios. Paliperidone plasma concentrations were simulated based on the estimates of the final population PK model using profiles from 5000 patients. The patient population for simulation was built by sampling, with replacement of demographic data from patients in the data set used for the development of PP1M<sup>4</sup> and PP3M models. PK simulations were performed in NONMEM version 7.3.0 and data management/processing of NONMEM output was performed using R 3.0.2 (NONMEM User Guides, Icon Development solutions, Ellicott City, Md.). The population median and 90% prediction interval of the simulated plasma concentration-time profiles were plotted and graphically presented to evaluate the outcome.

## Dosing Windows and Missed Doses

Simulations were performed to assess the dosing window during:

- switching from PP1M (150 or 50 mg eq.) to PP3M (525 or 175 mg eq.) at week 17 and with a  $\pm 1$  week dosing window; and
- maintenance therapy with PP3M (525 or 175 mg eq.) at regular week 12 and with a  $\pm 1$  to 3 week dosing window

18

The paliperidone plasma concentration—time profiles were also simulated for the missed dose scenarios when the third 525 mg eq. PP3M dose was missed and treatment was reinitiated depending on the duration since the last dose.

TABLE 4

Conversion between mg PP and mg eq. paliperidone for PP1M and PP3M

PP1M Dose (mg PP)	PP1M Dose (mg eq. Paliperidone)	PP3M Dose (mg PP)	PP3M Dose (mg eq. Paliperidone)
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

PP, paliperidone palmitate;  
PP3M, PP 3-month formulation;  
PP1M, PP 1-month formulation.

TABLE 5

Dosing reinitiation regimen for the missed dose simulations

Time interval of missed dose	Reinitiation treatment
<4 months	Continue PP3M Q12W
4-9 months	treatment reinitiated with 2 PP1M deltoid injections separated by one week, followed by PP3M dosing Q12W
>9 months	150 mg eq. PP1M deltoid injection on day 1 and 100 mg eq. PP1M deltoid injection on day 8, followed by 3 additional PP1M injections, before continuing PP3M dosing Q12W

Furthermore, paliperidone plasma concentrations versus time after stopping multiple PP3M doses were simulated.

## Assessment of Q12W Vs Q13W

Finally, simulations were also performed to compare Q12W vs Q13W dosing at steady state with PP3M and to demonstrate the impact of actual 3 months dosing (13 weeks) on paliperidone levels.

## Results:

In FIG. 1 the switching from PP1M to PP3M at a default of week 17 $\pm 1$  week resulting in:

TABLE 6

Window		$C_{min}$ (ng/mL)
+1 week	Reference	11.6
50 mg eq. PP1M Switched to 175 mg eq. PP3M dose	Modified	10.2
-1 week	Reference	58.2
150 mg eq. PP1M Switched to 525 mg eq. PP3M dose	Modified	60.2

As illustrated by FIG. 1 switching from 50 mg eq. PP1M to 175 mg eq. PP3M at Week 18 instead of Week 17 led to a decrease in  $C_{min}$  from 11.6 ng/mL to 10.2 ng/mL, and switching from 150 mg eq. PP1M to 525 mg eq. PP3M at Week 16 instead of Week 17 led to an increase in  $C_{max}$  from 58.2 ng/mL to 60.2 ng/mL. These changes in plasma concentrations are relatively small when a  $\pm 1$  week window is allowed at the time of switching from PP1M to PP3M.

In FIGS. 2A-2B the PP3M with a 12 week dosing week was modeled. In FIG. 2A the -X week simulations were performed with the highest PP3M dose strength of 525 mg eq. to simulate a worst-case scenario (i.e., largest % increase in  $C_{max}$ ).

EXPERTS\_MYL\_002390

US 10,143,693 B2

19

TABLE 7

525 mg eq. PP3M	$C_{max}$ (ng/mL)
Reference	56.4
Modified (-1 week)	57.1
Modified (-2 week)	58.0
Modified (-3 week)	58.8

In FIG. 2B) the +X week simulations were performed with the lowest PP3M dose strength of 175 mg eq. to simulate a worst-case scenario (i.e., largest % drop in  $C_{min}$ ) since the lowest dose has the shortest apparent  $t_{1/2}$ .

TABLE 8

175 mg eq. PP3M	$C_{min}$ (ng/mL)
Reference	11.0
Modified (+1 week)	10.3
Modified (+2 week)	9.7
Modified (+3 week)	9.0

After stabilization on PP3M, administration of 175 mg eq. PP3M:

- 1 week later than the scheduled:  $C_{min}$  decreased by 0.7 ng/mL
- 2 weeks later than the scheduled:  $C_{min}$  decreased by 1.3 ng/mL
- 3 weeks later than the scheduled:  $C_{min}$  decreased by 2.0 ng/mL

After stabilization on PP3M, administration of 525 mg eq. PP3M,

- 1 week earlier than scheduled:  $C_{max}$  increased by 0.7 ng/mL
- 2 weeks earlier than scheduled:  $C_{max}$  increased by 1.6 ng/mL
- 3 weeks earlier than the scheduled:  $C_{max}$  increased by 2.4 ng/mL

FIG. 2B illustrates the simulations done with 12 weeks with a maximum possible window of +3 weeks. However, 3 months is 13 weeks hence the simulations illustrates 3 months+2 week window. These changes in plasma concentrations are relatively small and justify a  $\pm 3$  week window for Q12W administration of PP3M, which corresponds to a  $\pm 2$  week window for Q13W (i.e. every 3 months) administration.

FIG. 4A-4C illustrate the predicted plasma concentration of PP3M (525 mg. eq.) at various time intervals. Similar paliperidone plasma outcomes were observed for other dosage strengths. Similar paliperidone plasma concentration as before the missed dose was achieved by the following reinitiation treatment:

PP3M missed by <4 months, treatment reinitiated with regular PP3M injections

PP3M missed between 4-9 months, treatment reinitiated with 2 PP1M deltoid injections separated by one week, followed by PP3M dosing Q12W using the regimen described in the table below:

20

TABLE 9

Re-initiation regimen after missing $\geq 4$ months up to 9 months of PP3M				
Last PP3M	Administer PP1M, two doses one week apart (into deltoid muscle)		Then administer PP3M (into deltoid <sup>a</sup> or gluteal muscle)	
dose	Day 1	Day 8	1 month after day 8	
175 mg eq.	50 mg eq.	→ 50 mg eq.	→ 175 mg eq.	
263 mg eq.	75 mg eq.	→ 75 mg eq.	→ 263 mg eq.	
350 mg eq.	100 mg eq.	→ 100 mg eq.	→ 350 mg eq.	
525 mg eq.	100 mg eq.	→ 100 mg eq.	→ 525 mg eq.	

PP3M missed for >9 months, treatment reinitiated with PP1M for 4 months before continuation of PP3M Q12W

Concentration of  $\geq 7.5$  ng/mL was maintained up to 10 to 14 months after the discontinuation of 350 and 525 mg eq. PP3M.

Paliperidone concentration of 7.5 ng/mL is associated with 60%  $D_2$  receptor occupancy, and is thought to be required for antipsychotic efficacy<sup>5</sup>. These simulations therefore support re-initiation with at least 4 months of treatment with PP1M (before transitioning to PP3M) if a maintenance dose of PP3M is missed for more than 9 months.

Additional simulations also showed a similar outcome with other dose strengths (data not shown).

What is claimed is:

1. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with a 3-month injectable paliperidone palmitate depot (PP3M), wherein said patient had been last administered a PP3M injection more than 9 months ago, and the next scheduled maintenance dose of the PP3M should be administered to said patient, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of 150 mg eq. of monthly injectable paliperidone palmitate depot (PP1M);
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of 100 mg eq. of PP1M on about the 4th day to about the 12th day after administering said first reinitiation loading dose;
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a first reinitiation maintenance dose of 50 mg eq. of PP1M on about the 23th day to about the 37th day after administering said second reinitiation loading dose;
- (4) administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering of the first reinitiation maintenance dose;
- (5) administering intramuscularly in the deltoid or gluteal muscle of said patient a third reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering of the second reinitiation maintenance dose; and
- (6) administering intramuscularly in the deltoid or gluteal muscle of said patient from about 175 mg eq. to about 525 mg eq. of PP3M on about the 23rd day to about the

EXPERTS\_MYL\_002391



US 10,143,693 B2

21

37th day after administering of the last reinitiation maintenance dose of monthly injectable paliperidone palmitate.

2. The method of claim 1, wherein said patient is in need of treatment for psychosis.

3. The method of claim 1, wherein said patient is in need of treatment for schizophrenia.

4. The method of claim 1, wherein said patient is in need of treatment for bipolar disorder.

5. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with PP3M, wherein said patient had been last administered a PP3M injection 4 to 9 months ago and the next scheduled maintenance dose of PP3M should be administered to said patient, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M;
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose; and
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose

Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M
175 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	525 mg eq.

6. The method of claim 5, wherein said patient is in need of treatment for psychosis.

7. The method of claim 5, wherein said patient is in need of treatment for schizophrenia.

8. The method of claim 5, wherein said patient is in need of treatment for bipolar disorder.

9. The method of claim 5 wherein the second reinitiation dose of PP1M is administered about 7 days after administering said first reinitiation loading dose of PP1M.

10. The method of claim 9 wherein the second reinitiation dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.

11. The method of claim 5 wherein the reinitiation dose of PP3M is administered about 30 days after administering said second reinitiation loading dose of PP1M.

12. The method of claim 11 wherein the reinitiation dose of PP3M is administered 30 days after administering said second reinitiation loading dose of PP1M.

13. The method of claim 5 wherein the reinitiation dose of PP3M is administered about a month after administering said second reinitiation loading dose of PP1M.

22

14. The method of claim 11 wherein the reinitiation dose of PP3M is administered a month after administering said second reinitiation loading dose of PP1M.

15. The method of claim 1 wherein the second reinitiation loading dose of PP1M is administered about 7 days after administering said first reinitiation loading dose of PP1M.

16. The method of claim 15 wherein the second reinitiation loading dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.

17. The method of claim 1 wherein the first reinitiation maintenance dose of PP1M is administered about 30 days after administering said second reinitiation loading dose of PP1M.

18. The method of claim 1 wherein the first reinitiation maintenance dose of PP1M is administered 30 days after administering said second reinitiation loading dose of PP1M.

19. The method of claim 1 wherein the second reinitiation maintenance of PP1M is administered about 30 days after administering said first reinitiation maintenance dose of PP1M.

20. The method of claim 1 wherein the second reinitiation maintenance of PP1M is administered 30 days after administering said first reinitiation maintenance dose of PP1M.

21. The method of claim 1 wherein the third reinitiation maintenance of PP1M is administered about 30 days after administering said second reinitiation maintenance dose of PP1M.

22. The method of claim 1 wherein the third reinitiation maintenance of PP1M is administered 30 days after administering said second reinitiation maintenance dose of PP1M.

23. The method of claim 1 wherein PP3M is administered about 30 days after administering said last reinitiation maintenance of PP1M.

24. The method of claim 1 wherein PP3M is administered 30 days after administering said last reinitiation maintenance of PP1M.

25. The method of claim 1 wherein PP3M is administered about a month after administering said last reinitiation maintenance of PP1M.

26. The method of claim 1 wherein PP3M is administered a month after administering said last reinitiation maintenance of PP1M.

27. The method of claim 1 further comprising administering intramuscularly in the deltoid or gluteal muscle of said patient a fourth reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering the third reinitiation maintenance dose.

28. The method of claim 27 wherein said fourth reinitiation maintenance of PP1M is administered about 30 days after administering said third reinitiation maintenance dose of PP1M.

29. The method of claim 28 wherein said fourth reinitiation maintenance of PP1M is administered 30 days after administering said third reinitiation maintenance dose of PP1M.

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**U.S. District Court  
District of New Jersey [LIVE] (Newark)  
CIVIL DOCKET FOR CASE #: 2:20-cv-13103-EP-LDW**

JANSSEN PHARMACEUTICALS, INC et al v MYLAN  
LABORATORIES LIMITED et al  
Assigned to Judge Evelyn Padin  
Referred to: Magistrate Judge Leda D. Wettre  
Case in other court: Federal Circuit, 23-02042  
Cause 15 1126 Patent Infringement

Date Filed 09/23/2020  
Date Terminated: 05/23/2023  
Jury Demand None  
Nature of Suit: 835 Patent - Abbreviated  
New Drug Application(ANDA)  
Jurisdiction: Federal Question

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*TERMINATED: 09/24/2020*

**Defendant**

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*TERMINATED: 09/24/2020*

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*ATTORNEY TO BE NOTICED*

**Counter Defendant**

**JANSSEN PHARMACEUTICALS, INC.**

represented by **KEITH J. MILLER**  
(See above for address)  
*ATTORNEY TO BE NOTICED*

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

**Counter Defendant****JANSSEN RESEARCH &  
DEVELOPMENT, LLC**represented by **KEITH J. MILLER**  
(See above for address)  
*ATTORNEY TO BE NOTICED*

Date Filed	#	Docket Text
09/23/2020	<a href="#"><u>1</u></a>	COMPLAINT against MYLAN INSTITUTIONAL LLC, MYLAN LABORATORIES LIMITED, MYLAN PHARMACEUTICALS, INC. ( Filing and Admin fee \$ 400 receipt number ANJDC-11397455), filed by JANSSEN PHARMACEUTICALS, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC, JANSSEN PHARMACEUTICA NV. (Attachments: # <a href="#"><u>1</u></a> Exhibit A, # <a href="#"><u>2</u></a> Civil Cover Sheet)(MILLER, KEITH) (Entered: 09/23/2020)
09/24/2020		Judge Brian R Martinotti and Magistrate Judge Lois H Goodman added (abr, ) (Entered 09/24/2020)
09/24/2020	<a href="#"><u>2</u></a>	AO120 Patent Form filed. (abr, ) (Entered: 09/24/2020)
09/24/2020	<a href="#"><u>3</u></a>	SUMMONS ISSUED as to MYLAN INSTITUTIONAL LLC, MYLAN LABORATORIES LIMITED. Attached is the official court Summons, please fill out Defendant and Plaintiffs attorney information and serve (abr) (Entered 09/24/2020)
09/24/2020	<a href="#"><u>4</u></a>	Letter from Keith J. Miller, Esq. to the Hon. Brian R. Martinotti, U.S.D.J. re Proposed Stipulation and Order Dismissing Without Prejudice Certain Defendants. (Attachments: # <a href="#"><u>1</u></a> Text of Proposed Order)(MILLER, KEITH) (Entered: 09/24/2020)
09/24/2020	<a href="#"><u>5</u></a>	STIPULATION AND ORDER of dismissal as to MYLAN INSTITUTIONAL LLC and MYLAN PHARMACEUTICALS, INC without prejudice Signed by Judge Brian R Martinotti on 09/24/2020. (jdb) (Entered: 09/24/2020)
09/25/2020	<a href="#"><u>6</u></a>	Corporate Disclosure Statement by JANSSEN PHARMACEUTICA NV, JANSSEN PHARMACEUTICALS, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC identifying Johnson & Johnson as Corporate Parent.. (MILLER, KEITH) (Entered: 09/25/2020)
10/01/2020	<a href="#"><u>7</u></a>	NOTICE of Appearance by ARNOLD B. CALMANN on behalf of MYLAN LABORATORIES LIMITED (CALMANN, ARNOLD) (Entered 10/01/2020)
10/01/2020	<a href="#"><u>8</u></a>	NOTICE of Appearance by JEFFREY S. SOOS on behalf of MYLAN LABORATORIES LIMITED (SOOS, JEFFREY) (Entered: 10/01/2020)
10/01/2020	<a href="#"><u>9</u></a>	NOTICE of Appearance by KATHERINE ANN ESCANLAR on behalf of MYLAN LABORATORIES LIMITED (ESCANLAR, KATHERINE) (Entered: 10/01/2020)
10/01/2020	<a href="#"><u>10</u></a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. Regarding Application On Consent for the Pro Hac Vice Admission of Deepto R. Mukerjee, Esq., Lance A. Soderstrom, Esq., Jitendra Malik, Ph.D., Esq., and Guylaine Hache, Ph.D., Esq. on Behalf of Mylan Laboratories Limited. (Attachments: # <a href="#"><u>1</u></a> Certification of Arnold B. Calmann, Esq., # <a href="#"><u>2</u></a> Declaration of Deepto R. Mukerjee, Esq., # <a href="#"><u>3</u></a> Declaration of Lance A. Soderstrom, Esq., # <a href="#"><u>4</u></a> Declaration of Jitendra Malik, Esq., # <a href="#"><u>5</u></a> Declaration of Guylaine Hache, Esq., # <a href="#"><u>6</u></a> Text of Proposed Order)(CALMANN, ARNOLD) (Entered: 10/01/2020)
10/05/2020	<a href="#"><u>11</u></a>	ORDER granting pro hac vice admission as to Deepto R. Mukerjee, Esq. and Lance A. Soderstrom, Esq Signed by Magistrate Judge Lois H Goodman on 10/05/2020 (jdb)

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

		(Entered: 10/05/2020)
10/06/2020	<a href="#">12</a>	Notice of Request by Pro Hac Vice Deepro R. Mukerjee, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-11461548.) (CALMANN, ARNOLD) (Entered: 10/06/2020)
10/06/2020	<a href="#">13</a>	Notice of Request by Pro Hac Vice Lance A. Soderstrom, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-11461578.) (CALMANN, ARNOLD) (Entered: 10/06/2020)
10/06/2020	<a href="#">14</a>	Notice of Request by Pro Hac Vice Jitendra Malik, Ph.D., Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-11461701.) (CALMANN, ARNOLD) (Entered: 10/06/2020)
10/06/2020	<a href="#">15</a>	Notice of Request by Pro Hac Vice Guylaine Hache, Ph.D., Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-11461739.) (CALMANN, ARNOLD) (Entered: 10/06/2020)
10/06/2020	<a href="#">16</a>	Application and Proposed Order for Clerk's Order to extend time to answer as to Plaintiffs' Complaint.. (CALMANN, ARNOLD) (Entered: 10/06/2020)
10/06/2020		Pro Hac Vice counsel, GUYLAINE HACHE, DEEPRO R. MUKERJEE, JITENDRA MALIK and LANCE A. SODERSTROM, has been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (abr, ) (Entered: 10/06/2020)
10/06/2020		Clerk`s Text Order - The document <a href="#">16</a> Application for Clerk's Order to Ext Answer/Proposed Order submitted by MYLAN LABORATORIES LIMITED has been GRANTED. The answer due date has been set for 11/2/2020. (abr, ) (Entered: 10/06/2020)
10/19/2020	<a href="#">17</a>	NOTICE of Change of Address by ARNOLD B. CALMANN (CALMANN, ARNOLD) (Entered: 10/19/2020)
11/02/2020	<a href="#">18</a>	ANSWER to Complaint , <i>Separate Defenses</i> , COUNTERCLAIM against JANSSEN PHARMACEUTICA NV, JANSSEN PHARMACEUTICALS, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> Certificate of Service)(CALMANN, ARNOLD) (Entered: 11/02/2020)
11/02/2020	<a href="#">19</a>	Corporate Disclosure Statement by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 11/02/2020)
11/06/2020	<a href="#">20</a>	Letter from Keith J. Miller, Esq. to Hon. Lois Goodman, U.S.M.J. re Pro Hac Vice Admissions. (Attachments: # <a href="#">1</a> Declaration of Keith J. Miller, # <a href="#">2</a> Declaration of Barbara Mullin, # <a href="#">3</a> Declaration of Aron Fisher, # <a href="#">4</a> Declaration of Andrew Cohen, # <a href="#">5</a> Text of Proposed Order)(MILLER, KEITH) (Entered: 11/06/2020)
11/09/2020	<a href="#">21</a>	ORDER granting pro hac vice admission as to Andrew D. Cohen, Esq., Barbara Lynn Mullin, Esq., and Aron Fischer, Esq. Signed by Magistrate Judge Lois H. Goodman on 11/09/2020. (jdb) (Entered: 11/09/2020)
11/10/2020	<a href="#">22</a>	Notice of Request by Pro Hac Vice Andrew D. Cohen, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-11630807.) (MILLER, KEITH) (Entered: 11/10/2020)
11/10/2020	<a href="#">23</a>	Notice of Request by Pro Hac Vice Barbara Lynn Mullin, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-11630842.) (MILLER, KEITH) (Entered: 11/10/2020)



9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

11/10/2020	<a href="#">24</a>	Notice of Request by Pro Hac Vice Aron Fischer, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-11630863.) (MILLER, KEITH) (Entered: 11/10/2020)
11/10/2020		Pro Hac Vice counsel, REW D. COHEN, BARBARA L. MULLIN and ARON FISCHER, has been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (jem) (Entered: 11/10/2020)
11/20/2020	<a href="#">25</a>	ANSWER to Counterclaim by All Plaintiffs.(MILLER, KEITH) (Entered: 11/20/2020)
12/02/2020	<a href="#">26</a>	Corporate Disclosure Statement by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 12/02/2020)
03/16/2021	<a href="#">27</a>	Order Initial Conference set for 4/21/2021 10:00 AM via Telephone Conference before Magistrate Judge Lois H. Goodman. The Court will provide counsel with dial in information prior to the scheduled conference. Signed by Magistrate Judge Lois H. Goodman on 3/16/2021. (if, ) (Entered: 03/16/2021)
04/21/2021		Text Minute Entry for proceedings held before Magistrate Judge Lois H. Goodman: Initial Pretrial Conference held on 4/21/2021 via Telephone Conference. (ijf, ) (Entered: 04/23/2021)
04/22/2021	<a href="#">28</a>	Discovery Confidentiality Order filed. Signed by Magistrate Judge Lois H. Goodman on 4/22/2021. (abr, ) (Entered: 04/22/2021)
04/26/2021	<a href="#">29</a>	Letter from Keith J. Miller, Esq. Regarding Application On Consent for the Pro Hac Vice Admission of Lachlan Campbell-Verduyn, Esq., J. Jay Cho, Esq., and A. Robert Quirk, Esq.. (Attachments: # <a href="#">1</a> Declaration of Keith J. Miller, Esq., # <a href="#">2</a> Declaration of Lachlan Campbell-Verduyn, Esq., # <a href="#">3</a> Declaration of J. Jay Cho, Esq., # <a href="#">4</a> Declaration of A. Robert Quirk, Esq., # <a href="#">5</a> Text of Proposed Order)(MILLER, KEITH) (Entered: 04/26/2021)
05/07/2021	<a href="#">30</a>	PRETRIAL SCHEDULING ORDER: Telephone Conference set for 6/15/2021 at 11:30 AM before Magistrate Judge Lois H. Goodman; Final Pretrial Conference set for 9/1/2022 10:00 AM before Magistrate Judge Lois H. Goodman; Any motion to amend the pleadings or join new parties must be with leave of Court and filed no later than 7/23/2021. Signed by Magistrate Judge Lois H. Goodman on 5/7/2021. (abr, ) (Entered: 05/07/2021)
06/04/2021	<a href="#">31</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. Regarding Application (On Consent) for the Pro Hac Vice Admission of Jillian M. Schurr, Esq. on behalf of Mylan Laboratories Limited. (Attachments: # <a href="#">1</a> Certification of Arnold B. Calmann, Esq., # <a href="#">2</a> Declaration of Jillian M. Schurr, Esq., # <a href="#">3</a> Text of Proposed Order) (CALMANN, ARNOLD) (Entered: 06/04/2021)
06/14/2021	32	TEXT ORDER rescheduling the 6/15/2021 Telephone Conference with Magistrate Judge Lois H. Goodman to 8/16/2021 at 3:00 p.m. So Ordered by Magistrate Judge Lois H. Goodman on 6/14/2021. (ijf, ) (Entered: 06/14/2021)
06/28/2021	33	TEXT ORDER REASSIGNING CASE. Case reassigned to Judge Zahid N. Quraishi for all further proceedings. Judge Brian R. Martinotti no longer assigned to case. So Ordered by Chief Judge Freda L. Wolfson on 6/28/2021. (jmh) (Entered: 06/28/2021)
07/01/2021	<a href="#">34</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. Requesting Approval of Withdrawal of Pro Hac Vice Attorney, Guylaine Hache, Esq. re <a href="#">11</a> Order. (CALMANN, ARNOLD) (Entered: 07/01/2021)

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

07/16/2021	<a href="#">35</a>	ORDER granting admission pro hac vice as to Jillian M. Schurr. Signed by Magistrate Judge Lois H Goodman on 7/16/2021 (mg) (Entered: 07/16/2021)
07/16/2021	<a href="#">36</a>	LETTER ORDER granting withdrawal of Guylaine Hache as counsel of record for MLL in this matter. Signed by Magistrate Judge Lois H. Goodman on 7/16/2021. (mg) (Entered: 07/16/2021)
07/19/2021	<a href="#">37</a>	Notice of Request by Pro Hac Vice Jillian M. Schurr, Esq. to receive Notices of Electronic Filings ( Pro Hac Vice fee \$ 150 receipt number ANJDC 12640761 ) (CALMANN, ARNOLD) (Entered: 07/19/2021)
07/19/2021		Pro Hac Vice counsel, JILLIAN M. SCHURR, has been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (abr, ) (Entered: 07/19/2021)
07/29/2021	<a href="#">38</a>	JOINT STIPULATION AND ORDER modifying Pretrial Scheduling Order. Signed by Magistrate Judge Lois H Goodman on 7/29/2021 (abr, ) (Entered: 07/29/2021)
08/13/2021	39	TEXT ORDER rescheduling the Telephone Conference scheduled for 8/16/2021 to 11/30/2021 at 3:30 p.m. with Magistrate Judge Lois H. Goodman. So Ordered by Magistrate Judge Lois H. Goodman on 8/13/2021. (ijf, ) (Entered: 08/13/2021)
09/10/2021	<a href="#">40</a>	Letter from Keith J. Miller, Esq. to Hon. Zahid N. Quraishi, U.S.D.J. and Hon. Lois Goodman, U S M J re <a href="#">38</a> Stipulation and Order (MILLER, KEITH) (Entered: 09/10/2021)
11/29/2021		ATTENTION COUNSEL: The 11/30/2021 Telephone Conference with Magistrate Judge Lois H. Goodman has been rescheduled to 1/3/2022 at 9:30 a.m. The Court will provide counsel with the dial in information prior to the scheduled conferenc. (ijf, ) (Entered: 11/29/2021)
12/03/2021	<a href="#">41</a>	Letter from Keith J. Miller, Esq. to Hon. Lois H. Goodman, U.S.M.J. enclosing application for the pro hac vice admission of Joyce L Nadipuram, Esq (Attachments # <a href="#">1</a> Declaration of Keith J. Miller, Esq., # <a href="#">2</a> Declaration of Joyce L. Nadipuram, Esq., # <a href="#">3</a> Text of Proposed Order)(MILLER, KEITH) (Entered: 12/03/2021)
12/13/2021	<a href="#">42</a>	ORDER granting pro hac vice admissions as to Joyce L. Nadipuram. Signed by Magistrate Judge Lois H. Goodman on 12/13/2021. (abr, ) (Entered: 12/13/2021)
12/15/2021	<a href="#">43</a>	Notice of Request by Pro Hac Vice Joyce L Nadipuram, Esq to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-13044233.) (MILLER, KEITH) (Entered: 12/15/2021)
12/15/2021	<a href="#">44</a>	ORDER granting pro hac vice as to Lachlan Campbell-Verduyn, J. Jay Cho, and A. Robert Quirk. Signed by Magistrate Judge Lois H. Goodman on 12/15/2021. (abr, ) (Entered: 12/15/2021)
12/17/2021		Pro Hac Vice counsel, JOYCE L. NADIPURAM, has been added to receive Notices of Electronic Filing Pursuant to L Civ R 101 1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (jal, ) (Entered: 12/17/2021)
01/03/2022		Text Minute Entry for proceedings held before Magistrate Judge Lois H. Goodman: Telephone Conference held on 1/3/2022. (ijf, ) (Entered: 01/04/2022)
01/04/2022	45	TEXT ORDER by 1/14/2022 each side is to submit an ex parte statement as to their position regarding settlement and whether parties believe a Settlement Conference would be productive Counsel are directed to submit consolidation order as to the three related

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

		cases by 1/24/2022. Telephone Conference set for 4/26/2022 at 11:00 a.m. with Magistrate Judge Lois H. Goodman. Plaintiffs' counsel to initiate the call at that time. So Ordered by Magistrate Judge Lois H. Goodman on 1/4/2022. (ijf, ) (Entered: 01/04/2022)
01/05/2022	<a href="#">46</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. Regarding Application on Consent for the Pro Hac Vice Admission of Joseph Michael Janusz, Esq.. (Attachments: # <a href="#">1</a> Certification of Arnold B. Calmann, Esq., # <a href="#">2</a> Declaration of Joseph Michael Janusz, Esq., # <a href="#">3</a> Text of Proposed Order)(CALMANN, ARNOLD) (Entered: 01/05/2022)
01/06/2022	<a href="#">47</a>	Letter from Keith J. Miller, Esq. to Hon. Zahid Quraishi, U.S.D.J. re Proposed Consolidation Order. (Attachments: # <a href="#">1</a> Text of Proposed Order)(MILLER, KEITH) (Entered: 01/06/2022)
01/07/2022	<a href="#">48</a>	STIPULATION AND ORDER consolidating cases for all purposes. Signed by Judge Zahid N. Quraishi on 1/7/2022. (abr, ) (Entered: 01/07/2022)
01/11/2022	<a href="#">49</a>	AMENDED PRETRIAL SCHEDULING ORDER: Trial has been rescheduled to 10/3/2022 at 10:00 AM. Signed by Magistrate Judge Lois H. Goodman on 1/11/2022. (abr, ) (Entered: 01/11/2022)
01/25/2022	<a href="#">50</a>	ORDER granting pro hac vice admissions as to Joseph Michael Janusz, Esq. Signed by Magistrate Judge Lois H. Goodman on 1/25/2022. (abr, ) (Entered: 01/25/2022)
01/25/2022	<a href="#">51</a>	Notice of Request by Pro Hac Vice Joseph Michael Janusz, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-13137681.) (CALMANN, ARNOLD) (Entered: 01/25/2022)
01/26/2022		Pro Hac Vice counsel, JOSEPH MICHAEL JANUSZ, has been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (abr, ) (Entered: 01/26/2022)
03/03/2022	<a href="#">52</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. Enclosing Proposed Amended Scheduling Order Extending the Deadlines for the Exchange of Expert Reports re <a href="#">30</a> Scheduling Order,. (Attachments: # <a href="#">1</a> Text of Proposed Order)(CALMANN, ARNOLD) (Entered: 03/03/2022)
03/09/2022	<a href="#">53</a>	AMENDED SCHEDULING ORDER extending deadlines for exchange of expert reports. Signed by Magistrate Judge Lois H. Goodman on 3/8/2022. (abr, ) (Entered: 03/09/2022)
04/01/2022	<a href="#">54</a>	NOTICE by MYLAN LABORATORIES LIMITED <i>of Change of Address of Pro Hac Vice Attorney</i> (CALMANN, ARNOLD) (Entered: 04/01/2022)
04/11/2022	55	TEXT ORDER REASSIGNING CASE. Case reassigned to Judge Georgette Castner for all further proceedings. Judge Zahid N. Quraishi no longer assigned to case. So Ordered by Chief Judge Freda L. Wolfson on 4/11/2022. (dm ) (Entered: 04/11/2022)
04/26/2022		TEXT Minute Entry for proceedings held before Magistrate Judge Lois H. Goodman: Telephone Conference held on 4/26/2022. (eh, ) (Entered: 04/26/2022)
04/26/2022	56	TEXT ORDER: Counsel are to report by 4/29/22 on their efforts to resolve the invalidity contentions/expert issue. If they are unable to resolve it, they are to submit a joint letter by 5/6/22. The Court will conduct a Telephone Status Conference on 6/15/2022 at 11:00 AM. So Ordered by Magistrate Judge Lois H. Goodman on 4/26/2022. (eh, ) (Entered: 04/26/2022)

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

04/27/2022	57	TEXT ORDER: A Status Conference is set for 5/9/2022 at 11:00 AM in Trenton - Courtroom 4E before Judge Georgette Castner. The parties are to submit to the Court a joint status report one week prior to the conference not to exceed 5 pages. So Ordered by Judge Georgette Castner on 4/27/22. (adi, ) (Entered: 04/27/2022)
05/02/2022	58	TEXT ORDER: Parties' request of a one-day extension of time to submit to the Court on 5/3/2022 a joint status report is hereby granted. So Ordered by Judge Georgette Castner on 5/2/2022. (adi, ) (Entered: 05/02/2022)
05/03/2022	<a href="#">59</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Georgette Castner, U.S.D.J. Regarding Joint Status Report re 57 Order,, Set Hearings, 58 Order. (CALMANN, ARNOLD) (Entered: 05/03/2022)
05/05/2022	<a href="#">60</a>	Notice of Request by Pro Hac Vice A. Robert Quirk, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-13390158.) (MILLER, KEITH) (Entered: 05/05/2022)
05/05/2022	<a href="#">61</a>	Notice of Request by Pro Hac Vice Jay Cho, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-13390175.) (MILLER, KEITH) (Entered: 05/05/2022)
05/05/2022	<a href="#">62</a>	Notice of Request by Pro Hac Vice Lachlan S. Campbell-Verduyn, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-13390189.) (MILLER, KEITH) (Entered: 05/05/2022)
05/06/2022		Pro Hac Vice counsel, A. ROBERT QUIRK, JAY J. CHO and LACHLAN CAMPBELL-VERDUYN, has been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (jdg) (Entered: 05/06/2022)
05/09/2022		Text Minute Entry for proceedings held before Judge Georgette Castner: Status Conference held on 5/9/2022. Not on the record. (adi, ) (Entered: 05/09/2022)
05/11/2022	<a href="#">63</a>	Consent MOTION to Dismiss ( <i>Partial</i> ) by All Plaintiffs. Responses due by 5/23/2022 (Attachments: # <a href="#">1</a> Brief, # <a href="#">2</a> Text of Proposed Order)(MILLER, KEITH) (Entered: 05/11/2022)
05/11/2022		Set Deadlines as to <a href="#">63</a> Consent MOTION to Dismiss ( <i>Partial</i> ). Motion set for 6/6/2022 before Judge Georgette Castner. Unless otherwise directed by the Court, this motion will be decided on the papers and no appearances are required. Note that this is an automatically generated message from the Clerk's Office and does not supersede any previous or subsequent orders from the Court. (abr, ) (Entered: 05/11/2022)
05/26/2022	<a href="#">64</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Georgette Castner, U.S.D.J. and the Honorable Lois H. Goodman, U.S.M.J. Regarding Tutorial and Final Pretrial Conference. (CALMANN, ARNOLD) (Entered: 05/26/2022)
06/03/2022	<a href="#">65</a>	ORDER granting <a href="#">63</a> Motion to Partially Dismiss; Plaintiff's claims of infringement of claims 1-3 and 15-29 of the 693 Patent based on the Mylan and ANDAs are dismissed with prejudice; Mylan's counterclaims for a declaratory judgment of non-infringement and invalidity as to claims 1-3 and 15-29 of the 693 Patent are dismissed as moot. Signed by Judge Georgette Castner on 6/2/2022. (abr, ) (Entered: 06/03/2022)
06/06/2022	<a href="#">66</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. Regarding Application On Consent for the Pro Hac Vice Admission of Brian Sodikoff, Esq. on Behalf of Defendant Mylan. (Attachments: # <a href="#">1</a> Certification of Arnold B. Calmann, Esq., # <a href="#">2</a> Declaration of Brian Sodikoff, Esq., # <a href="#">3</a> Text of Proposed Order) (CALMANN, ARNOLD) (Entered: 06/06/2022)

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

06/07/2022	<a href="#">67</a>	ORDER granting pro hac vice admissions as to Brian Sodikoff. Signed by Magistrate Judge Lois H. Goodman on 6/7/2022. (abr, ) (Entered: 06/07/2022)
06/09/2022	<a href="#">68</a>	Notice of Request by Pro Hac Vice Brian Sodikoff, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-13473518.) (CALMANN, ARNOLD) (Entered: 06/09/2022)
06/10/2022		Pro Hac Vice counsel, BRIAN SODIKOFF, has been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (abr, ) (Entered: 06/10/2022)
06/15/2022		Text Minute Entry for proceedings held before Magistrate Judge Lois H. Goodman: Telephone Conference held on 6/15/2022. (ijf, ) (Entered: 06/21/2022)
06/21/2022	<a href="#">69</a>	AMENDED PRETRIAL SCHEDULING ORDER: Final Pretrial Conference is adjourned to 9/8/2022 at 12:00 PM before Judge Lois H. Goodman . Counsel are to report on the status of any settlement discussions by no later than 6/17/2022. Signed by Magistrate Judge Lois H. Goodman on 6/21/2022. (jdg) Modified on 6/22/2022 (jmh). (Entered: 06/21/2022)
06/23/2022	<a href="#">70</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. Requesting Extension of Time to Submit Joint Dispute Letter Regarding Expert Report re <a href="#">69</a> Scheduling Order,. (CALMANN, ARNOLD) (Entered: 06/23/2022)
06/28/2022	<a href="#">71</a>	LETTER ORDER extending deadline to submit joint letter regarding the scope of defendant's expert report to 6/28/2022. Signed by Magistrate Judge Lois H. Goodman on 6/28/2022. (abr, ) (Entered: 06/28/2022)
06/28/2022	<a href="#">72</a>	Letter from Keith J. Miller, Esq. to Hon. Lois Goodman, U.S.M.J. re Infringement Contentions Dispute. (Attachments: # <a href="#">1</a> Exhibit 1, # <a href="#">2</a> Exhibit 2, # <a href="#">3</a> Exhibit 3, # <a href="#">4</a> Exhibit 4, # <a href="#">5</a> Exhibit 5, # <a href="#">6</a> Exhibit 6, # <a href="#">7</a> Exhibit 7, # <a href="#">8</a> Exhibit 8, # <a href="#">9</a> Exhibit 9, # <a href="#">10</a> Exhibit 10, # <a href="#">11</a> Exhibit A, # <a href="#">12</a> Exhibit B, # <a href="#">13</a> Exhibit C, # <a href="#">14</a> Exhibit D)(MILLER, KEITH)  <a href="#">NOTICE TO COUNSEL</a> : Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court. (Entered: 06/28/2022)
07/11/2022	73	TEXT ORDER granting the parties' joint request to extend the deadline for expert discovery to be completed by 8/10/2022. So Ordered by Magistrate Judge Lois H. Goodman on 7/11/2022. (ijf, ) (Entered: 07/11/2022)
07/12/2022	<a href="#">74</a>	REDACTION to <a href="#">72</a> Letter,,, by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> UNREDACTED Exhibit 1, # <a href="#">2</a> REDACTED Exhibit 2, # <a href="#">3</a> REDACTED Exhibit 3, # <a href="#">4</a> UNREDACTED Exhibit 4, # <a href="#">5</a> REDACTED Exhibit 5, # <a href="#">6</a> REDACTED Exhibit 6, # <a href="#">7</a> UNREDACTED Exhibit 7, # <a href="#">8</a> UNREDACTED Exhibit 8, # <a href="#">9</a> UNREDACTED Exhibit 9, # <a href="#">10</a> UNREDACTED Exhibit 10, # <a href="#">11</a> REDACTED Exhibit A, # <a href="#">12</a> REDACTED Exhibit B, # <a href="#">13</a> UNREDACTED Exhibit C, # <a href="#">14</a> REDACTED Exhibit D)(CALMANN, ARNOLD) (Entered: 07/12/2022)
07/12/2022	<a href="#">75</a>	Joint MOTION to Seal Document <a href="#">72</a> Letter,,, by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> Declaration of Preston Imperatore in support of Motion to Seal, # <a href="#">2</a> Exhibit 1 - Index in support of Motion to Seal, # <a href="#">3</a> Statement of Keith J. Miller, Esq. in support of Motion to Seal, # <a href="#">4</a> Index in support of Motion to Seal, # <a href="#">5</a> Text of Proposed Order, # <a href="#">6</a> Certificate of Service)(CALMANN, ARNOLD) (Entered: 07/12/2022)

9/20



9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

07/13/2022		Set Deadlines as to <a href="#">75</a> Joint MOTION to Seal Document <a href="#">72</a> Letter,,. Motion set for 8/15/2022 before Magistrate Judge Lois H. Goodman. Unless otherwise directed by the Court, this motion will be decided on the papers and no appearances are required. Note that this is an automatically generated message from the Clerk's Office and does not supersede any previous or subsequent orders from the Court. (abr, ) (Entered: 07/13/2022)
07/28/2022	<a href="#">76</a>	AMENDED PRETRIAL SCHEDULING ORDER: Parties are to file any motion in limine by no later than 45 days before trial. Signed by Magistrate Judge Lois H. Goodman on 7/27/2022. (abr, ) (Entered: 07/28/2022)
08/04/2022	<a href="#">77</a>	ORDER granting <a href="#">75</a> Motion to Seal Document <a href="#">75</a> Joint MOTION to Seal Document <a href="#">72</a> Letter,,. Signed by Magistrate Judge Lois H. Goodman on 8/4/2022. (mg) (Entered: 08/04/2022)
08/04/2022	<a href="#">78</a>	LETTER ORDER that Janssen's request to strike portions of Dr. Berger's rebuttal report is denied without prejudice; Janssen may file the appropriate motion in limine in accordance with timeline as set by the Court for such motions. Signed by Magistrate Judge Lois H. Goodman on 8/4/2022. (mg) (Entered: 08/04/2022)
08/09/2022	<a href="#">79</a>	Letter from Keith J. Miller, Esq. to Hon. Georgette Castner, U.S.D.J. re Pretrial Briefs. (MILLER, KEITH) (Entered: 08/09/2022)
08/19/2022	<a href="#">80</a>	MOTION in Limine Nos. 1-3 by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> Text of Proposed Order Motion in Limine No. 1, # <a href="#">2</a> Text of Proposed Order Motion in Limine No. 2, # <a href="#">3</a> Text of Proposed Order Motion in Limine No. 3, # <a href="#">4</a> Certificate of Service)(CALMANN, ARNOLD) (Entered: 08/19/2022)
08/19/2022	<a href="#">81</a>	MOTION in Limine by All Plaintiffs. (Attachments: # <a href="#">1</a> Brief, # <a href="#">2</a> Declaration of Keith J. Miller, # <a href="#">3</a> Exhibit 1, # <a href="#">4</a> Exhibit 2, # <a href="#">5</a> Exhibit 3, # <a href="#">6</a> Text of Proposed Order)(MILLER, KEITH) (Entered: 08/19/2022)
08/19/2022	<a href="#">82</a>	BRIEF in Support filed by MYLAN LABORATORIES LIMITED re <a href="#">80</a> MOTION in Limine Nos. 1-3 <i>Motion in Limine No. 1 to Preclude Evidence of a Single Entity Direct Infringer</i> (CALMANN, ARNOLD)  <a href="#">NOTICE TO COUNSEL</a> : Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court. (Entered: 08/19/2022)
08/19/2022	<a href="#">83</a>	BRIEF in Support filed by MYLAN LABORATORIES LIMITED re <a href="#">80</a> MOTION in Limine Nos. 1-3 <i>Motion in Limine No. 2 to Exclude Evidence of Alleged Commercial Success of Invega Trinza by Ms. Carla Mulhern</i> (CALMANN, ARNOLD)  <a href="#">NOTICE TO COUNSEL</a> : Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court. (Entered: 08/19/2022)
08/19/2022	<a href="#">84</a>	BRIEF in Support filed by MYLAN LABORATORIES LIMITED re <a href="#">80</a> MOTION in Limine Nos. 1-3 <i>Motion in Limine No. 3 to Preclude Argument, Evidence, or Testimony That Was Not Previously Disclosed Regarding the Prior Art Status of JAMA</i> (CALMANN, ARNOLD)  <a href="#">NOTICE TO COUNSEL</a> : Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials

10/20

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

		sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court (Entered: 08/19/2022)
08/19/2022	<a href="#">85</a>	DECLARATION of Jillian M. Schurr, Esq. in Support of Mylan's Motions In Limine Nos. 1-3 re <a href="#">83</a> Brief in Support of Motion,, <a href="#">82</a> Brief in Support of Motion,, <a href="#">80</a> MOTION in Limine Nos. 1-3, <a href="#">84</a> Brief in Support of Motion,, by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 08/19/2022)
08/19/2022	<a href="#">86</a>	Exhibit to <a href="#">85</a> Declaration, <i>Exhibits 1 8 to the Declaration of Jillian M Schurr, Esq</i> by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> Exhibit 9-16 to the Declaration of Jillian M Schurr, Esq in support of Mylan's Motions in Limine Nos 1 3) (CALMANN, ARNOLD)  <a href="#">NOTICE TO COUNSEL</a> : Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court. (Entered: 08/19/2022)
08/19/2022		Clerk's Note: Doc. <a href="#">81</a> was sealed at the request of counsel. (jr) (Entered: 08/19/2022)
08/22/2022		Set Deadlines as to <a href="#">80</a> MOTION in Limine Nos 1 3, <a href="#">81</a> MOTION in Limine Motion set for 9/19/2022 before Judge Georgette Castner. Unless otherwise directed by the Court, this motion will be decided on the papers and no appearances are required Note that this is an automatically generated message from the Clerk's Office and does not supersede any previous or subsequent orders from the Court (mg) (Entered: 08/22/2022)
08/31/2022	<a href="#">87</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Georgette Castner, U.S.D.J. Regarding Mylan's Motion In Limine No. 3. (CALMANN, ARNOLD) (Entered: 08/31/2022)
09/02/2022	<a href="#">88</a>	NOTICE by MYLAN LABORATORIES LIMITED <i>Pursuant to 35 U.S.C. Section 282</i> (Attachments # <a href="#">1</a> Certificate of Service)(CALMANN, ARNOLD) (Entered: 09/02/2022)
09/02/2022	<a href="#">89</a>	BRIEF in Opposition filed by All Plaintiffs re <a href="#">80</a> MOTION in Limine Nos. 1-3 ( <i>Motion in Limine No. 1</i> ) (MILLER, KEITH)  <a href="#">NOTICE TO COUNSEL</a> : Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court. (Entered: 09/02/2022)
09/02/2022	<a href="#">90</a>	BRIEF in Opposition filed by All Plaintiffs re <a href="#">80</a> MOTION in Limine Nos 1 3 ( <i>Motion in Limine No. 2</i> ) (Attachments: # <a href="#">1</a> Declaration of Keith J. Miller, # <a href="#">2</a> Exhibit 1, # <a href="#">3</a> Exhibit 2)(MILLER, KEITH)  <a href="#">NOTICE TO COUNSEL</a> : Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court (Entered: 09/02/2022)
09/02/2022	<a href="#">91</a>	BRIEF in Opposition filed by MYLAN LABORATORIES LIMITED re <a href="#">81</a> MOTION in Limine (Attachments: # <a href="#">1</a> Exhibit A, # <a href="#">2</a> Exhibit B, # <a href="#">3</a> Exhibit C)(CALMANN, ARNOLD)  <a href="#">NOTICE TO COUNSEL</a> : Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court. (Entered: 09/02/2022)

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

09/02/2022	<a href="#">92</a>	DECLARATION of of Jillian M. Schurr, Esq. in Support of Mylan's Opposition to Plaintiffs' Motion In Limine re <a href="#">91</a> Brief in Opposition to Motion,, by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> Certificate of Service)(CALMANN, ARNOLD) (Entered: 09/02/2022)
09/08/2022		Text Minute Entry for proceedings held before Magistrate Judge Lois H. Goodman: Final Pretrial Conference held on 9/8/2022. (ijf, ) (Entered: 09/13/2022)
09/08/2022	<a href="#">94</a>	Minute Entry for proceedings held before Judge Georgette Castner: Technology tutorial presentation held on 9/8/2022. Parties are to submit briefs addressing certain topics by 9/19/2022. (Court Reporter, Frank Gable (856-889-4761)) (adi, ) (Entered: 09/14/2022)
09/12/2022	<a href="#">93</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. Regarding Application on Consent for the Pro Hac Vice Admission of Christopher W. West, Esq. and Rachel J. Schaub, Esq. on behalf of Mylan. (Attachments: # <a href="#">1</a> Certification of Arnold B. Calmann, Esq., # <a href="#">2</a> Declaration of Christopher W. West, Esq., # <a href="#">3</a> Declaration of Rachel J. Schaub, Esq., # <a href="#">4</a> Text of Proposed Order)(CALMANN, ARNOLD) (Entered: 09/12/2022)
09/16/2022	<a href="#">95</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Lois H. Goodman, U.S.M.J. on Behalf of the Parties Requesting Extension of Time to File Motion to Seal and Redacted Documents re <a href="#">83</a> Brief in Support of Motion,, <a href="#">82</a> Brief in Support of Motion,, <a href="#">89</a> Brief in Opposition to Motion,, <a href="#">90</a> Brief in Opposition to Motion,, <a href="#">86</a> Exhibit (to Document),, <a href="#">91</a> Brief in Opposition to Motion,, <a href="#">81</a> MOTION in Limine , <a href="#">84</a> Brief in Support of Motion,, (CALMANN, ARNOLD) (Entered: 09/16/2022)
09/19/2022	<a href="#">96</a>	TRIAL BRIEF ( <i>JOINT</i> ) REGARDING LEGAL STANDARDS by JANSSEN PHARMACEUTICA NV, JANSSEN PHARMACEUTICALS, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC. (MILLER, KEITH) (Entered: 09/19/2022)
09/20/2022		Set/Reset Hearings: Pretrial Motion Hearing re: <a href="#">80</a> MOTION in Limine Nos. 1-3 by MYLAN LABORATORIES LIMITED & <a href="#">81</a> MOTION in Limine by All Plaintiffs set for 9/27/2022 at 11:00 AM in Trenton - Courtroom 4E before Judge Georgette Castner. (adi, ) (Entered: 09/20/2022)
09/21/2022	<a href="#">97</a>	LETTER ORDER granting extension to file motion to seal and redacted documents due 9/30/2022. Signed by Magistrate Judge Lois H. Goodman on 9/21/2022. (kht) (Entered: 09/21/2022)
09/21/2022		Set/Reset Hearings: Telephone Conference re: Trial Scheduling set for 9/22/2022 at 01:00 PM before Judge Georgette Castner. The dial in information has been provided to the parties. (adi, ) (Entered: 09/21/2022)
09/22/2022	<a href="#">98</a>	ORDER granting admission pro hac vice as to Christopher W. West. Signed by Magistrate Judge Lois H. Goodman on 9/22/2022. (mg) (Entered: 09/22/2022)
09/22/2022		Text Minute Entry for proceedings held before Judge Georgette Castner: Trial Scheduling Conference held on 9/22/2022 via telephone. Parties are to meet and confer then submit a revised schedule to the Court by 9/27/22. Not on the record. (adi) (Entered: 09/22/2022)
09/23/2022	<a href="#">99</a>	FINAL PRETRIAL ORDER. Signed by Magistrate Judge Lois H. Goodman on 9/22/2022. (mg) (Entered: 09/23/2022)
09/23/2022	<a href="#">100</a>	Notice of Request by Pro Hac Vice Christopher W. West, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-13708721.) (CALMANN, ARNOLD) (Entered: 09/23/2022)
09/23/2022	<a href="#">101</a>	Notice of Request by Pro Hac Vice Rachel J. Schaub, Esq. to receive Notices of Electronic Filings. ( Pro Hac Vice fee \$ 150 receipt number ANJDC-13708744.)

12/20



9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

		(CALMANN, ARNOLD) (Entered: 09/23/2022)
09/23/2022	<a href="#">102</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Georgette Castner, U.S.D.J. Regarding Mylan's Motion In Limine No. 2 re <a href="#">83</a> Brief in Support of Motion,, (CALMANN, ARNOLD) (Entered: 09/23/2022)
09/26/2022		Pro Hac Vice counsel, CHRISTOPHER W. WEST and RACHEL J. SCHAUB, has been added to receive Notices of Electronic Filing. Pursuant to L.Civ.R. 101.1, only local counsel are entitled to sign and file papers, enter appearances and receive payments on judgments, decrees or orders. (kht) (Entered: 09/26/2022)
09/26/2022		Set/Reset Hearings: Please be advised that the 9/27/2022 Pretrial Motion Hearing has been reset to 9/30/2022 at 11:00 AM via Video Conference before Judge Georgette Castner. (adi, ) (Entered: 09/26/2022)
09/27/2022	<a href="#">103</a>	ORDER recusing Judge Georgette Castner. Clerk is directed to randomly reassign case. Signed by Judge Georgette Castner on 9/27/2022. (mg) (Entered: 09/27/2022)
09/28/2022	104	TEXT ORDER REALLOCATING AND REASSIGNING CASE. Case reallocated to Newark and reassigned to Judge Evelyn Padin for all further proceedings. Judge Georgette Castner no longer assigned to case. So Ordered by Chief Judge Freda L. Wolfson on 9/28/2022. (jjc, ) (Entered: 09/28/2022)
09/28/2022	<a href="#">114</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Status Conference held on 9/28/2022. (bt) (Entered: 09/30/2022)
09/30/2022	<a href="#">105</a>	REDACTION to <a href="#">81</a> MOTION in Limine by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> REDACTED Brief in Support of Plaintiffs' Motion In Limine, # <a href="#">2</a> UNREDACTED Declaration of Keith J. Miller, Esq., # <a href="#">3</a> REDACTED Exhibit 1, # <a href="#">4</a> REDACTED Exhibit 2, # <a href="#">5</a> REDACTED Exhibit 3, # <a href="#">6</a> UNREDACTED Proposed Order)(CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">106</a>	REDACTION to <a href="#">82</a> Brief in Support of Motion,, by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">107</a>	REDACTION to <a href="#">83</a> Brief in Support of Motion,, <i>UNREDACTED BRIEF</i> by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">108</a>	REDACTION to <a href="#">84</a> Brief in Support of Motion,, by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">109</a>	REDACTION to <a href="#">86</a> Exhibit (to Document),, by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> REDACTED Exhibits 9-16)(CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">110</a>	REDACTION to <a href="#">89</a> Brief in Opposition to Motion,, by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">111</a>	REDACTION to <a href="#">90</a> Brief in Opposition to Motion,, <i>UNREDACTED BRIEF</i> by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> UNREDACTED Declaration of Keith J. Müller, Esq., # <a href="#">2</a> UNREDACTED Exhibit 1, # <a href="#">3</a> UNREDACTED Exhibit 2) (CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">112</a>	REDACTION to <a href="#">91</a> Brief in Opposition to Motion,, by MYLAN LABORATORIES LIMITED. (Attachments: # <a href="#">1</a> REDACTED Exhibit A, # <a href="#">2</a> UNREDACTED Exhibit B, # <a href="#">3</a> UNREDACTED Exhibit C)(CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">113</a>	Joint MOTION to Seal Document <a href="#">81</a> MOTION in Limine , <a href="#">91</a> Brief in Opposition to Motion,, <a href="#">84</a> Brief in Support of Motion,, <a href="#">86</a> Exhibit (to Document),, <a href="#">89</a> Brief in Opposition to Motion,, <a href="#">82</a> Brief in Support of Motion,, by MYLAN LABORATORIES

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

		LIMITED. (Attachments: # <a href="#">1</a> Declaration of Preston Imperatore, Esq., # <a href="#">2</a> Exhibit 1, # <a href="#">3</a> Declaration of Keith J. Miller, Esq., # <a href="#">4</a> Exhibit 2, # <a href="#">5</a> Text of Proposed Order) (CALMANN, ARNOLD) (Entered: 09/30/2022)
09/30/2022	<a href="#">115</a>	LETTER ORDER scheduling an In-Person Conference for 10/20/2022 at 10:30 AM regarding issues and oral argument on the remaining motions in limine. Signed by Judge Evelyn Padin on 9/30/2022. (dam) (Entered: 09/30/2022)
10/05/2022		Set Deadlines as to <a href="#">113</a> Joint MOTION to Seal Document <a href="#">81</a> MOTION in Limine, <a href="#">91</a> Brief in Opposition to Motion, <a href="#">84</a> Brief in Support of Motion, <a href="#">86</a> Exhibit (to Document), <a href="#">89</a> Brief in Opposition to Motion, <a href="#">82</a> Brief in Support of Motion. Motion set for 11/7/2022 before Magistrate Judge Lois H. Goodman. Unless otherwise directed by the Court, this motion will be decided on the papers and no appearances are required. Note that this is an automatically generated message from the Clerk's Office and does not supersede any previous or subsequent orders from the Court. (dam, ) (Entered: 10/05/2022)
10/07/2022	<a href="#">116</a>	REDACTION to <a href="#">99</a> Order by All Plaintiffs. (MILLER, KEITH) (Entered: 10/07/2022)
10/07/2022	<a href="#">117</a>	Joint MOTION to Seal <i>Final Pretrial Order</i> by All Plaintiffs. (Attachments: # <a href="#">1</a> Text of Proposed Order, # <a href="#">2</a> Statement of Keith J. Miller, # <a href="#">3</a> Index to Miller Statement, # <a href="#">4</a> Declaration of Preston Imperatore, Esq., # <a href="#">5</a> Index to Imperatore Declaration)(MILLER, KEITH) (Entered: 10/07/2022)
10/11/2022		Minute Entry for proceedings held before Judge Evelyn Padin: Scheduling Conference held on 10/11/2022. (bt) (Entered: 10/11/2022)
10/11/2022	<a href="#">118</a>	ORDER granting <a href="#">113</a> Motion to Seal Document <a href="#">113</a> Joint MOTION to Seal Document <a href="#">81</a> MOTION in Limine , <a href="#">91</a> Brief in Opposition to Motion,, <a href="#">84</a> Brief in Support of Motion,, <a href="#">86</a> Exhibit (to Document),, <a href="#">89</a> Brief in Opposition to Motion,, <a href="#">82</a> Brief in Support of Motion,, . Signed by Magistrate Judge Lois H. Goodman on 10/11/2022. (mg) (Entered: 10/11/2022)
10/12/2022	<a href="#">119</a>	ORDER granting <a href="#">117</a> Motion to Seal. Signed by Magistrate Judge Lois H. Goodman on 10/11/2022. (mg) (Entered: 10/12/2022)
10/20/2022	<a href="#">120</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Motion Hearing held on 10/20/2022 re <a href="#">80</a> MOTION in Limine <i>Nos. 1-3</i> filed by MYLAN LABORATORIES LIMITED and <a href="#">81</a> MOTION in Limine filed by JANSSEN PHARMACEUTICA NV. Both Motions denied for the reasons and to the extent on the record. (Court Reporter, Sara Killian) (bt) (Entered: 10/21/2022)
10/21/2022	<a href="#">121</a>	ORDER denying <a href="#">80</a> , <a href="#">81</a> Parties' Motions in Limine. Signed by Judge Evelyn Padin on 10/20/2022. (dam) (Entered: 10/21/2022)
10/21/2022	<a href="#">122</a>	SEALED STIPULATION AND ORDER. Signed by Judge Evelyn Padin on 10/21/2022. (dam) (Entered: 10/21/2022)
10/24/2022	<a href="#">123</a>	TEXT ORDER - The parties shall appear for a Zoom settlement conference before Magistrate Judge Leda D. Wettre on October 31, 2022 at 9:30 a.m. Log-in information will be circulated to counsel prior to that date. Clients with full and immediate settlement authority must attend for the duration. Confidential settlement letters, which shall not exceed ten (10) pages absent leave from the Court, shall be sent to LDW_orders@njd.uscourts.gov no later than October 27, 2022. Voluminous exhibits to settlement letters (exceeding 20 pages) will not be reviewed by the Court unless submitted in hard copy that is received by Chambers no later than three business days in advance of the settlement conference. So Ordered by Magistrate Judge Leda D. Wettre on 10/24/2022. (rn) (Entered: 10/24/2022)

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

10/26/2022	<a href="#">124</a>	STIPULATION AND ORDER regarding Rule 52(c) Motions. Signed by Judge Evelyn Padin on 10/26/2022. (dam) (Entered: 10/26/2022)
10/26/2022	<a href="#">125</a>	STIPULATION AND ORDER regarding Authenticity of Documents. Signed by Judge Evelyn Padin on 10/26/2022. (dam) (Entered: 10/26/2022)
10/31/2022		Minute Entry for proceedings held before Magistrate Judge Leda D. Wettre: Settlement Conference held on 10/31/2022. (LM, ) (Entered: 10/31/2022)
11/01/2022		Case Reassigned to Magistrate Judge Leda D. Wettre. Magistrate Judge Lois H. Goodman no longer assigned to the case. (ak, ) (Entered: 11/01/2022)
11/16/2022	<a href="#">127</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial held on 11/16/2022. (Court Reporter, Sara Killian (973-776-3885) (bt) (Entered: 11/21/2022)
11/17/2022	<a href="#">126</a>	Transcript of Tutorial held on 9/8/2022, before Judge Georgette Castner. Court Reporter/Transcriber Frank Gable (856-889-4761). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event 'Redact and Seal Transcript/Digital Recording'. Redaction Request to Court Reporter/Transcription Agency due, but not filed, by 12/8/2022. Redacted Transcript Deadline set for 12/19/2022. Release of Transcript Restriction set for 2/15/2023. (jdg, ) (Entered: 11/17/2022)
11/30/2022	<a href="#">128</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial Day 2 continued on 11/30/2022. (Court Reporter, Sara Killian (973-776-3885) (bt) (Entered: 12/01/2022)
12/01/2022	<a href="#">129</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial Day 3 continued on 12/1/2022. (Court Reporter, Sara Killian (973-776-3885) (bt) (Entered: 12/05/2022)
12/05/2022	<a href="#">130</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial Day 4 continued on 12/5/2022. (Court Reporter, Sara Killian (973-776-3885) (bt) (Entered: 12/06/2022)
12/06/2022	<a href="#">131</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial Day 5 continued on 12/6/2022. (Court Reporter, Sara Killian (973-776-3885) (bt) (Entered: 12/07/2022)
12/07/2022	<a href="#">132</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial Day 6 continued on 12/7/2022. (Court Reporter, Sara Killian (973-776-3885) (bt) (Entered: 12/08/2022)
12/08/2022	<a href="#">133</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial Day 7 continued on 12/8/2022. (Court Reporter, Sara Killian (973-776-3885) (bt) (Entered: 12/09/2022)
12/09/2022	<a href="#">134</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial Day 8 on 12/9/2022. (Court Reporter, Sara Killian (973-776-3885) (bt) Modified on 3/22/2023 (bt). (Entered: 12/12/2022)
01/24/2023	<a href="#">135</a>	TRIAL BRIEF -- <i>Mylan's Opening Post-Trial Brief</i> -- by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 01/24/2023)

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

01/24/2023	<a href="#">136</a>	Proposed Findings of Fact by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 01/24/2023)
01/24/2023	<a href="#">137</a>	TRIAL BRIEF ( <i>Post-Trial</i> ) by JANSSEN PHARMACEUTICA NV, JANSSEN PHARMACEUTICALS, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC. (MILLER, KEITH) (Entered: 01/24/2023)
01/24/2023	<a href="#">138</a>	Proposed Findings of Fact by JANSSEN PHARMACEUTICA NV, JANSSEN PHARMACEUTICALS, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC. (MILLER, KEITH) (Entered: 01/24/2023)
01/25/2023	<a href="#">139</a>	AMENDED DOCUMENT by MYLAN LABORATORIES LIMITED. Amendment to <a href="#">136</a> Proposed Findings of Fact -- <i>Corrected Mylan's Proposed Findings of Fact and Conclusions of Law</i> --. (CALMANN, ARNOLD)  <u>NOTICE TO COUNSEL:</u> Counsel is advised that pursuant to Local Civil Rule 5.3(c)(2), a single, consolidated motion to seal shall be filed within 14 days following the completed briefing of the materials sought to be sealed, or within 14 days following the date on which the last of such materials was filed under temporary seal if the motion is resolved, unless otherwise directed by the Court. (Entered: 01/25/2023)
01/25/2023	<a href="#">140</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Evelyn Padin, U.S.D.J. re <a href="#">136</a> Proposed Findings of Fact, <a href="#">139</a> Amended Document,,. (CALMANN, ARNOLD) (Entered: 01/25/2023)
02/21/2023	<a href="#">141</a>	TRIAL BRIEF ( <i>Plaintiffs' Responsive Post-Trial Brief</i> ) by JANSSEN PHARMACEUTICA NV, JANSSEN PHARMACEUTICALS, INC., JANSSEN RESEARCH & DEVELOPMENT, LLC. (MILLER, KEITH) (Entered: 02/21/2023)
02/21/2023	<a href="#">142</a>	TRIAL BRIEF -- <i>Mylan's Post-Trial Responsive Brief</i> -- by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 02/21/2023)
02/21/2023	<a href="#">143</a>	CERTIFICATE OF SERVICE by MYLAN LABORATORIES LIMITED re <a href="#">142</a> Trial Brief (CALMANN, ARNOLD) (Entered: 02/21/2023)
02/22/2023	144	TEXT ORDER: Closing arguments will be held in person on 3/16/2023 at 1:00 pm in Courtroom 4C in the Martin Luther King Building & U.S. Courthouse 50 Walnut Street Newark, NJ 07102. So Ordered by Judge Evelyn Padin on 2/22/2023. (bt) (Entered: 02/22/2023)
03/06/2023	<a href="#">145</a>	Letter from Arnold B. Calmann, Esq. to the Honorable Leda Dunn Wettre, U.S.M.J. Requesting Extension of Time to File Motion to Seal and Redacted Versions re <a href="#">142</a> Trial Brief, <a href="#">136</a> Proposed Findings of Fact, <a href="#">137</a> Trial Brief, <a href="#">139</a> Amended Document,, <a href="#">141</a> Trial Brief, <a href="#">138</a> Proposed Findings of Fact, <a href="#">135</a> Trial Brief. (CALMANN, ARNOLD) (Entered: 03/06/2023)
03/08/2023	<a href="#">146</a>	LETTER ORDER granting <a href="#">145</a> Joint Request for a two (2) week extension of time to file the redacted versions and a motion to seal related to the parties' post-trial filings from 3/7/2023 to 3/21/2023. Signed by Magistrate Judge Leda D. Wettre on 3/8/2023. (dam) (Entered: 03/08/2023)
03/16/2023	<a href="#">155</a>	Minute Entry for proceedings held before Judge Evelyn Padin: Bench Trial completed on 3/16/2023. (Court Reporter, Sara Killian (973-776-3885) (bt) (Entered: 03/22/2023)
03/21/2023	<a href="#">147</a>	REDACTION to <a href="#">137</a> Trial Brief by All Plaintiffs. (MILLER, KEITH) (Entered: 03/21/2023)
03/21/2023	<a href="#">148</a>	REDACTION to <a href="#">138</a> Proposed Findings of Fact by All Plaintiffs. (MILLER, KEITH) (Entered: 03/21/2023)



9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

03/21/2023	<a href="#">149</a>	REDACTION to <a href="#">135</a> Trial Brief by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 03/21/2023)
03/21/2023	<a href="#">150</a>	REDACTION to <a href="#">141</a> Trial Brief by All Plaintiffs. (MILLER, KEITH) (Entered: 03/21/2023)
03/21/2023	<a href="#">151</a>	REDACTION to <a href="#">136</a> Proposed Findings of Fact <i>and Conclusions of Law</i> by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 03/21/2023)
03/21/2023	<a href="#">152</a>	REDACTION to <a href="#">139</a> Amended Document,, <i>Corrected Proposed Findings of Fact and Conclusions of Law</i> by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 03/21/2023)
03/21/2023	<a href="#">153</a>	REDACTION to <a href="#">142</a> Trial Brief -- <i>Mylan's Post-Trial Responsive Brief--</i> by MYLAN LABORATORIES LIMITED. (CALMANN, ARNOLD) (Entered: 03/21/2023)
03/21/2023	<a href="#">154</a>	Joint MOTION to Seal Document ( <i>Post-Trial Briefing</i> ) by All Plaintiffs. (Attachments: # <a href="#">1</a> Statement of Keith J. Miller, Esq., # <a href="#">2</a> Index to Miller Statement, # <a href="#">3</a> Declaration of Preston Imperatore, Esq., # <a href="#">4</a> Index to Imperatore Declaration, # <a href="#">5</a> Text of Proposed Order)(MILLER, KEITH) (Entered: 03/21/2023)
03/22/2023		Set Deadlines as to <a href="#">154</a> Joint MOTION to Seal (Post-Trial Briefing). Motion set for 4/17/2023 before Magistrate Judge Leda D. Wettre. Unless otherwise directed by the Court, this motion will be decided on the papers and no appearances are required. Note that this is an automatically generated message from the Clerk's Office and does not supersede any previous or subsequent orders from the Court. (dam) (Entered: 03/22/2023)
04/04/2023	<a href="#">156</a>	ORDER granting <a href="#">154</a> Unopposed Joint Motion to Seal Portions of the Parties' Post-Trial Briefing. Signed by Magistrate Judge Leda D. Wettre on 4/4/2023. (dam) (Entered: 04/04/2023)
04/28/2023	<a href="#">157</a>	*REDACTED* Transcript of Bench Trial Vol 1 held on November 16, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event 'Redact and Seal Transcript/Digital Recording'. Redaction Request to Court Reporter due, but not filed, by 5/19/2023. Redacted Transcript Deadline set for 5/30/2023. Release of Transcript Restriction set for 7/27/2023. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">158</a>	**SEALED** Transcript of Bench Trial Vol 1 held on November 16, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). This is the complete unredacted/sealed version of the transcript and is unavailable for public viewing. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">159</a>	*REDACTED* Transcript of Bench Trial Vol 2 held on November 30, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event 'Redact and Seal Transcript/Digital Recording'. Redaction Request to Court Reporter: due, but not filed, by 5/19/2023.

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9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

		Redacted Transcript Deadline set for 5/30/2023. Release of Transcript Restriction set for 7/27/2023. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">160</a>	<b>**SEALED**</b> Transcript of Bench Trial Vol 2 held on November 30, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). This is the complete unredacted/sealed version of the transcript and is unavailable for public viewing. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">161</a>	Transcript of Bench Trial Vol 3 held on December 1, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event `Redact and Seal Transcript/Digital Recording`. Redaction Request to Court Reporter due, but not filed, by 5/19/2023. Redacted Transcript Deadline set for 5/30/2023. Release of Transcript Restriction set for 7/27/2023. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">162</a>	Transcript of Bench Trial Vol 4 held on December 5, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event `Redact and Seal Transcript/Digital Recording`. Redaction Request to Court Reporter due, but not filed, by 5/19/2023. Redacted Transcript Deadline set for 5/30/2023. Release of Transcript Restriction set for 7/27/2023. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">163</a>	<b>*REDACTED*</b> Transcript of Bench Trial Vol 5 held on December 6, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event `Redact and Seal Transcript/Digital Recording`. Redaction Request to Court Reporter due, but not filed, by 5/19/2023. Redacted Transcript Deadline set for 5/30/2023. Release of Transcript Restriction set for 7/27/2023. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">164</a>	<b>**SEALED**</b> Transcript of Bench Trial Vol 5 held on December 6, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). This is the complete unredacted/sealed version of the transcript and is unavailable for public viewing. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">165</a>	<b>*REDACTED*</b> Transcript of Bench Trial Vol 6 held on December 7, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

		utilizing the event `Redact and Seal Transcript/Digital Recording`. Redaction Request to Court Reporter due, but not filed, by 5/19/2023. Redacted Transcript Deadline set for 5/30/2023. Release of Transcript Restriction set for 7/27/2023. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">166</a>	<b>**SEALED**</b> Transcript of Bench Trial Vol 6 held on December 7, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). This is the complete unredacted/sealed version of the transcript and is unavailable for public viewing. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">167</a>	<b>*REDACTED*</b> Transcript of Bench Trial Vol 7 held on December 8, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event `Redact and Seal Transcript/Digital Recording`. Redaction Request to Court Reporter due, but not filed, by 5/19/2023. Redacted Transcript Deadline set for 5/30/2023. Release of Transcript Restriction set for 7/27/2023. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">168</a>	<b>**SEALED**</b> Transcript of Bench Trial Vol 7 held on December 8, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). This is the complete unredacted/sealed version of the transcript and is unavailable for public viewing. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">169</a>	<b>*REDACTED*</b> Transcript of Bench Trial Vol 8 held on December 9, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event `Redact and Seal Transcript/Digital Recording`. Redaction Request to Court Reporter due, but not filed, by 5/19/2023. Redacted Transcript Deadline set for 5/30/2023. Release of Transcript Restriction set for 7/27/2023. (adc) (Entered: 05/01/2023)
04/28/2023	<a href="#">170</a>	<b>**SEALED**</b> Transcript of Bench Trial Vol 8 held on December 9, 2022, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). This is the complete unredacted/sealed version of the transcript and is unavailable for public viewing. (adc) (Entered: 05/01/2023)
05/15/2023	<a href="#">171</a>	SEALED OPINION. Signed by Judge Evelyn Padin on 5/15/2023. (dam) (Entered: 05/15/2023)
05/15/2023	<a href="#">172</a>	ORDER directing the parties to submit a joint proposed form of judgment consistent with this Order and the accompanying Opinion within seven (7) days of this Order; directing the parties to submit a joint, proposed redacted version of the Court's Opinion, as well as a statement of reasons as to why each redaction is necessary, within seven (7) days of this Order. Janssen has demonstrated that Mylans Proposed ANDA Products will induce direct infringement of the 693 Patent. Mylan has failed to demonstrate that the Asserted Claims are invalid. Signed by Judge Evelyn Padin on 5/15/2023. (dam) (Entered: 05/15/2023)

9/11/23, 3:24 PM

CM/ECF LIVE - U.S. District Court for the District of New Jersey

05/23/2023	<a href="#">173</a>	REDACTED OPINION. Signed by Judge Evelyn Padin on 5/15/2023. (dam) (Entered: 05/23/2023)
05/23/2023	<a href="#">174</a>	FINAL JUDGMENT entered in favor of Janssen and against Mylan on all claims and counterclaims with respect to infringement and validity claims 5-7 and 9-14 of the '693 patent and Mylan's products that are the subject of ANDA Nos. 216228, 212290, and 215682. Signed by Judge Evelyn Padin on 5/23/2023. (dam) (Entered: 05/23/2023)
05/26/2023	<a href="#">175</a>	NOTICE OF APPEAL to Federal Circuit as to <a href="#">174</a> Order of Dismissal, <a href="#">171</a> Opinion by MYLAN LABORATORIES LIMITED. Filing fee \$ 505, receipt number ANJDC-14347664 The Clerk's Office hereby certifies the record and the docket sheet available through ECF to be the certified list in lieu of the record and/or the certified copy of the docket entries (Attachments # <a href="#">1</a> Certificate of Service)(CALMANN, ARNOLD) (Entered: 05/26/2023)
06/13/2023	<a href="#">176</a>	*REDACTED* Transcript of Jury Trial Vol 9 held on March 16, 2023, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). <b>NOTICE REGARDING (1) REDACTION OF PERSONAL IDENTIFIERS IN TRANSCRIPTS AND (2) MOTION TO REDACT AND SEAL:</b> The parties have seven (7) calendar days to file with the Court a Notice of Intent to Request Redaction of this Transcript to comply with Fed.R.Civ.P.5.2(a) (personal identifiers). Parties seeking to redact and seal this Transcript, or portions thereof, pursuant to L.Civ.R. 5.3(g) must e-file a Motion to Redact and Seal utilizing the event 'Redact and Seal Transcript/Digital Recording'. Redaction Request to Court Reporter due, but not filed, by 7/5/2023. Redacted Transcript Deadline set for 7/14/2023. Release of Transcript Restriction set for 9/11/2023. (adc) (Entered: 06/15/2023)
06/13/2023	<a href="#">177</a>	**SEALED** Transcript of Jury Trial Vol 9 held on March 16, 2023, before Judge Evelyn Padin. Court Reporter: Sara Killian (973-776-3885). This is the complete unredacted/sealed version of the transcript and is unavailable for public viewing (adc) (Entered: 06/15/2023)
06/20/2023	<a href="#">178</a>	USCA Case Number 23-2042 for <a href="#">175</a> Notice of Appeal (Federal Circuit), filed by MYLAN LABORATORIES LIMITED. (Document Restricted - Court Only) (adc, ) (Entered: 06/27/2023)
08/07/2023	<a href="#">179</a>	NOTICE by All Plaintiffs of <i>Withdrawal of A Robert Quirk as Pro Hac Vice Counsel</i> (MILLER, KEITH) (Entered: 08/07/2023)
08/07/2023	<a href="#">180</a>	ORDER of Withdrawal as to <i>Pro Hac Vice</i> Attorney A. ROBERT QUIRK. Signed by Magistrate Judge Leda D. Wettre on 8/7/2023. (dam) (Entered: 08/07/2023)

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PACER Login:	katten3278	Client Code:	391026-00331
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Billable Pages:	18	Cost:	1.80





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June 28, 2022

**VIA CM/ECF**

Hon. Lois H. Goodman, U.S.M.J.  
United States District Court, District of New Jersey  
Clarkson S. Fischer Federal Building & U.S. Courthouse

Re: Janssen Pharmaceuticals, Inc. et al v. Mylan Laboratories Ltd. 3:20-cv-13103 –  
Highly Confidential

Dear Judge Goodman:

This Firm, along with Patterson Belknap Webb & Tyler, represents Plaintiffs Janssen Pharmaceuticals, Inc., Janssen Pharmaceuticals NV, and Janssen Research & Development, LLC (collectively, “Janssen”) in the above action. As directed by Your Honor at the June 15, 2022 conference, enclosed on behalf of all parties is a joint letter concerning certain subject matter in Mylan’s rebuttal expert report on infringement.

**Janssen’s Position**

**I. Background of the Dispute**

This is a Hatch-Waxman case involving Janssen’s U.S. Patent No. 10,143,693 (the “693 Patent”), listed in the Orange Book for Janssen’s Invega Trinza® product. Invega Trinza is a long-acting injectable paliperidone palmitate antipsychotic medication that can be administered every three months. The Asserted Claims in the 693 Patent (claims 5-7 and 9-14) are to dosing regimens for treating psychiatric patients who had been receiving a three-month paliperidone palmitate (“PP3M”) injectable but have missed a dose – and whose last dose was given 4–9 months ago. The Asserted Claims recite a series of steps that include administering to these patients specific doses of one-month paliperidone palmitate (“PP1M”) and PP3M, at specific time intervals, by injection in specific locations. The dosing regimen of the Asserted Claims is set forth in the label instructions that are provided with Invega Trinza.

Mylan filed Abbreviated New Drug Applications seeking FDA approval to market generic versions of all four available dose strengths of Invega Trinza. Mylan copied the label instructions for Invega Trinza for its proposed generic product, including the missed dose instructions. Janssen then filed suit alleging induced infringement of the Asserted Claims.

When Mylan provided its non-infringement contentions over a year ago, it did not dispute that physicians or other healthcare providers (“HCPs”) would infringe the Asserted Claims by administering PP3M according to Mylan’s proposed label. Instead, Mylan contended that *Mylan* would not directly infringe (because Mylan itself does not administer any drug), and that *Mylan* would not induce infringement (despite its copied label instructions), because the label would not cause HCPs to administer the drug according to the missed dose regimen. *See* Ex. A at 4-6 (Mylan’s May 26, 2021 Non-Infringement Contentions). Janssen’s position, identified in its contentions and in its opening expert report on infringement, is that Mylan will indeed induce

infringement because its proposed label instructs HCPs to practice the Asserted Claims for patients who have missed a dose of PP3M and whose last dose was 4-9 months ago. This dispute as to whether Mylan's label induces infringement by HCPs has been identified for trial.

The present dispute concerns a different legal theory, which Mylan presented for the first time in its rebuttal expert report. Mylan's new theory is that the steps of the Asserted Claims are divided among multiple actors (*i.e.*, patients and their HCPs), such that there is no direct infringement by *anyone* (and therefore no induced infringement by Mylan) under the case law concerning "divided infringement."<sup>1</sup> This theory was not disclosed in Mylan's contentions and relies on a previously-undisclosed claim construction theory that was not addressed during the scheduled period for claim construction proceedings. *See* ECF No. 38 (setting claim construction deadlines between August 16, 2021 and October 12, 2021). Mylan's "divided infringement" theory should, accordingly, be stricken as untimely.

## II. Mylan's New "Divided Infringement" Theory

The premise of Mylan's new "divided infringement" theory is that the act of missing a dose is a step of the claimed dosing regimen. Based on this premise, Mylan contends that multiple entities are involved in the performance of the claimed missed dose regimens: (1) the HCPs who administer the injectables, and (2) the patient who misses the dose. Mylan further contends that the practice of the claimed dosing regimens does not constitute direct infringement by anyone because no single actor is responsible for practicing all the steps in the claims. Mylan first advanced this theory through its expert, Dr. Berger, in his rebuttal expert report on infringement. Ex. B at ¶¶ 57-65 (Berger Rebuttal Report).

Mylan's new theory has no merit because under the plain meaning of the claim language, missing a dose is not a step of the claimed dosing regimens. Indeed, the Asserted Claims do not refer to the act of missing a dose at all. Rather, they define the target population to be treated (patients who "had last been administered a PP3M injection 4 to 9 months ago"), and set forth a dosing regimen to be administered to these patients. While this target population is a required *element* of the claims, akin to contracting a disease or being diagnosed as overweight, it is not a *step* of the claimed dosing regimens. *See, e.g., Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.*, 282 F. Supp. 3d 793, 799, 812 (D. Del. 2017), *aff'd in part, rev'd in part sub nom. Nalpropion Pharmaceuticals, Inc. v. Actavis Labs. FL, Inc.*, 934 F.3d 1344 (Fed. Cir. 2019) (holding that diagnosis for overweight or obesity was not step of claim for method of treating overweight or obesity).<sup>2</sup> The steps of the claimed regimens therefore cannot be "divided" among multiple actors. Although Janssen understands that the present submission is not on the merits of the argument, it

<sup>1</sup> *See Akamai Tech., Inc. v. Limelight Networks*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (en banc).

<sup>2</sup> This is a common and rarely challenged structure for method of treatment claims: the claims cover a method of treatment for a specific population. For example, Mylan's U.S. Patent No. 9,949,933 includes claims to a "method of reducing a cholesterol level and/or increasing high-density lipoprotein levels in *a patient at risk of cardiovascular disease*, comprising administering a dosage form to said patient . . . ." Under Mylan's divided infringement theory, becoming "at risk of cardiovascular disease" would be the first step of the method of treatment claim.

is important to appreciate the unusual logic of Mylan's position to determine whether this theory was fairly disclosed and whether Janssen faces prejudice.

**A. Mylan's divided infringement theory was not disclosed in its non-infringement contentions**

As required by Local Patent Rule 3.6, Mylan served its non-infringement contentions on May 26, 2021. Mylan argued that it does not directly infringe the Asserted Claims because Mylan itself does not administer the claimed dosing regimen to the patient. *See, e.g.*, Ex. A at 4 ("Because Mylan would never administer any treatment, Mylan cannot directly infringe"). Mylan also contended that it does not induce infringement because it "does not have control over whether a subject is actually provided, treated, and/or administered the composition" and does not "induce any particular party to perform any particular claim step that Mylan itself does not practice, *i.e.*, administering a claimed composition." *Id.* at 5-6.

Critically, Mylan did **not** contend (1) that missing a dose was a step of the claimed dosing regimen or (2) that the Asserted Claims are not directly infringed under a "divided infringement" theory, because two actors (patient and doctor) are required to perform the steps of the claimed method. Indeed, Mylan's contentions include no discussion of missing a dose at all.

The local patent rules "exist to further the goal of full and timely discovery and provide all parties with adequate notice and information with which to litigate their case." *Celgene Corp. v. Hetero Labs*, 2021 U.S. Dist. LEXIS 159262, \*65 (D.N.J. March 29, 2021) (internal citations omitted). As this Court has previously explained, "[g]iven the purpose behind the patent local rules' disclosure requirements, a party may not use an expert report to introduce new infringement theories . . . not disclosed in the parties' infringement contentions. . . ." *Id.* at \*12 (internal citations omitted).

Mylan did not comply with the contention disclosure requirements of the local rules and Mylan's failure to disclose its theory prejudices Janssen. Because of the late disclosure, Janssen does not have sufficient time to address this novel legal theory through a motion for summary judgment. Janssen should not be put to the burden of addressing this new position that, if it had been timely disclosed, would already have been the subject of a summary judgment motion.

**B. Mylan's divided infringement theory is premised on a claim construction that it never advanced**

As noted, Mylan's divided infringement theory is premised on a claim construction that makes one of the steps of the claimed dosing regimen "the act of missing a dose" by the patient, such that (purportedly) "two actors [are] required to perform all of the steps of the claimed method." Ex. B at ¶¶ 57-58. If Mylan had advanced this theory in its contentions, as it was required to do, Janssen could have addressed Mylan's erroneous claim construction at the scheduled time. Instead, neither party proposed any terms for the Court to construe during claim construction or at any time leading up to Dr. Berger's rebuttal infringement report.

Janssen could not have anticipated Mylan's new claim construction. First, as noted above, Mylan's claim construction is inconsistent with the plain language of the claim and



standard approach of construing method-of-treatment claims and could not have been discerned by Janssen from the oblique language on which Mylan relies. Second, Mylan's new proposed claim construction is inconsistent with Mylan's earlier position regarding the meaning of the claims. Throughout this litigation, Mylan has consistently relied on the plain meaning of the claims as a method of treatment for a particular population of patients. For example, Mylan's primary expert, Dr. Forrest, opined in his opening expert report on validity that the preamble of the 693 Patent claims recites a "patient group" being treated by a "method." Ex. C at ¶¶ 217, 229. Similarly, in its Invalidity Contentions, Mylan described the preamble of the claims as defining the patient population. Mylan's Ex. 10 at 46, 63.

The purpose of contentions is precisely to avoid this situation, where Mylan has introduced a new infringement theory late in the case that Janssen has not had the opportunity to address at claim construction or otherwise.

### C. Mylan's arguments are meritless

In its submission below, Mylan does not (and cannot) contend that it disclosed a "divided infringement" theory or an "act of missing a dose" claim construction in its contentions. Instead, Mylan makes a handful of irrelevant arguments that Janssen briefly addresses here.

**First**, Mylan contends that because it "made clear that it was contesting indirect infringement at least in part because [it] would not induce 'another's direct infringement,'" Janssen should have been on notice that Mylan was asserting a "divided infringement" argument. But Mylan never made a "divided infringement" argument and Janssen had no reason to guess that it would seek to do so in the future. Mylan's statement that it would not "induce any particular party to perform any particular claim step that Mylan itself does not practice, *i.e.*, administering a claimed composition" does not disclose Mylan's present contentions that the "act of missing a dose" is a claim step, that a patient and a doctor are therefore both required to perform the steps of the Asserted Claims, or that, as a result, there is no **direct** infringement of the Asserted Claims by a single actor.<sup>3</sup>

**Second**, Mylan argues that Janssen's contentions and expert reports demonstrate that Janssen was, in fact, on notice of Mylan's new theory. But even assuming that Mylan could satisfy its disclosure obligations by relying on **Janssen's** submissions, nothing therein remotely reflects notice of Mylan's "divided infringement" theory. Mylan cites two statements from Janssen's contentions: "direct infringers under § 271(a) include physicians, other healthcare providers, and/or patients who administer the Accused Instrumentality," and, "Mylan's Proposed Label is specifically designed to instruct and direct physicians, other healthcare providers and/or patients to administer Mylan's proposed generic product." But these statements simply list out

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<sup>3</sup> *Chiesi USA, Inc. v. Aurobindo Pharma USA, Inc.*, No. 19-18756-ZNQ-LHG, 2022 WL 304574, at \*7 (D.N.J. Jan. 9, 2022), on which Mylan relies, is inapposite. There, the Court permitted a defendant to argue that the plaintiff had failed to present experimental evidence of infringement because defendant could not have anticipated the evidence plaintiff would rely on. Here, Mylan is asserting a novel **legal theory** that it could have disclosed in its contentions.



individuals who might **administer** the proposed generic product by following Mylan's proposed label. They recognize that anyone who administers the missed dose instructions in Mylan's proposed label – whether an HCP or a patient – will directly infringe the Asserted Claims.<sup>4</sup> Neither of these statements nor anything else in Janssen's contentions suggests that Janssen was on notice of Mylan's argument that two actors are required to practice the Asserted Claims because the "act of missing a dose" is a step of the claims.

**Third**, Mylan's argument that Janssen's expert, Dr. Sommi, opined "that two entities are required for direct infringement" is equally wrong. In the paragraph cited by Mylan, Dr. Sommi explains that "for patients who have missed a dose of PP3M, and whose last dose of PP3M was administered 4 to 9 months ago, Mylan's Proposed Label instructs **healthcare professionals**" to follow the claimed dosing regimen. Dr. Sommi does not state or suggest that the "act of missing a dose" is a step of the dosing regimen.

**Fourth**, Mylan argues that Janssen has delayed in bringing the issue to the Court. In addition to being irrelevant, this argument is incorrect. Janssen promptly brought the untimeliness of the theory to Mylan's attention on May 11, 2022, two days after Mylan served its expert report. Thereafter, the parties exchanged emails on the issue on May 13 (Mylan), May 18 (Janssen), May 26 (Mylan), and June 3 (Janssen). The parties met and conferred on June 8 and Janssen raised the issue at the scheduled June 15, 2022 status conference. *See* Ex. D.

**Finally**, Mylan seeks to change the subject, accusing Janssen of relying on documents in its expert report that were not timely provided to Mylan. This is, of course, completely irrelevant to the issue at hand, which concerns Mylan's failure to disclose a noninfringement theory. In any event, should Mylan choose to meet and confer with Janssen and pursue this issue, Janssen will show that its contentions, unlike Mylan's, were fully compliant with the Local Rules.

#### **D. Conclusion**

Trial is scheduled to begin on October 3, 2022 – just a few months from now. This is not the appropriate time to inject new theories into the case. It would be contrary to the Local Rules and would subvert the ordered schedule for a timely claim construction process to allow Mylan to introduce new theories now. Janssen would be prejudiced if it is forced to prepare for trial on this newly disclosed defense. Accordingly, Janssen respectfully requests that the Court strike Dr. Berger's opinions on divided infringement as untimely.

### **Mylan's Position**

#### ***1. Mylan's Response on the "Background of the Dispute."***

Under the guise of a discovery dispute, Plaintiffs argue what is essentially an unwarranted MIL, alleging that Mylan be stripped of one of its non-infringement arguments set forth during the

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<sup>4</sup> Although Invega Trinza® is typically administered by healthcare providers, the Asserted Claims are not limited as to administrator.



contentions phase. But, the hallmark of contentions is notice, and Plaintiffs have been on notice of Mylan's non-infringement positions since the nascent stages of this case. Though they feign surprise, Plaintiffs obviously were on notice because they put forth substantive responses to Mylan's contentions and an infringement theory from its expert that took these into account. Further, the parties have only begun expert depositions with a single expert (unrelated to infringement) having been deposed to date. Thus, Plaintiffs will have ample opportunity to attempt to prove their infringement theory and test the underpinnings of Mylan's experts' opinions.

Plaintiffs devote considerable real estate providing a skewed view of the patent at issue and the case. The claims of the '693 patent are not "standard" "method-of-treatment claims" as Plaintiffs mistakenly suggest. Although the '693 patent is listed in the Orange Book for Invega Trinza®, the labeled indication (*i.e.*, treatment of a patient with PP3M who has been treated with PP1M for at least 4 months) is **not** covered by the claims. This is not a "common structure for method of treatment claims" and Plaintiffs' attempt at analogizing the '693 claims to those in cases regarding "contracting a disease" or actively initiating treatment, has no merit. In the '693 patent prosecution history, Plaintiffs argued that missing a dose *is* "required" by the claim limitations. Ex. 1 at 4, Applicants' Resp. ("The instant claims are **solely** directed to **what patients** should **do** if a dose is missed and **they** [**the patient**] desires getting back on the medication." (emphasis added)).

Finally, suggesting for the first time that there is a purported claim construction issue only undermines Plaintiffs' positions before the patent office, and throughout this litigation to date.<sup>5</sup> The claims require no construction. Mylan's position on non-infringement is clear and Plaintiffs responded acknowledging those positions and putting forth their infringement theory. The parties have now moved into expert discovery and their respective experts are addressing those positions.

## ***2. Mylan's Contentions Put Plaintiffs on Notice and Complied with the Local Rules.***

Mylan denied that it infringed the claims of the '693 patent, both directly and indirectly. Its contentions state, "Mylan does not cause, urge, encourage, aid, advise, or otherwise induce **any particular party** to practice **any particular claim step** that Mylan, itself, does not practice, *i.e.*, treating a subject having a disorder." Ex. A at 4. But, Mylan is not relying on that isolated

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<sup>5</sup> Plaintiffs now take the position that "missing a dose is not a step of the claimed dosing regimens"; yet Janssen has listed the '693 patent in the Orange Book for Invega Trinza® with Use Codes that solely speak to "reinitiation" of treatment "**following a missed dose.**" Based on Plaintiffs' new arguments, Mylan reserves the right to seek leave to amend its Answer to add a Delisting Counterclaim. Further, this also goes against what Janssen's fact witnesses and expert have testified to date. *See* Ex. 2, Sommi Report at ¶¶ 60, 43; Ex. 3, Dep. Tr. of A. Russu at 25:14-16 ("Q: When it says 'fails to take the next scheduled dose,' who is that referring to? A: The said patient, in my understanding."); Ex. 4, Dep. Tr. of S. Gopal at 80:16-22 ("Q: And certainly you can't force a patient to come into an office at any given time for treatment? A: That is correct."). If a patient does not miss a dose, there is no infringement. Likewise, if a patient does not return for treatment within 4 to 9 months of the last dose, there is no infringement.

contention alone. Mylan also put Plaintiffs on notice of their burden that a single party must directly infringe for there to be indirect infringement, including by reiterating the proper legal standard that “[d]irect infringement requires that a single party’s activities meet all the limitations claimed. To infringe a claim comprising a series of steps, ‘a person must have practiced all steps’ of the claim.” *Id.* at 4-5 (quoting *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1317 (Fed. Cir. 2009)).<sup>6</sup> And, again, Mylan stated that it “does not and will not directly instruct physicians or anyone else to practice, much less infringe, the Asserted Claims.” Ex. A at 6. As such, even at the nascent stages of this litigation, Mylan made clear that it was contesting indirect infringement because it—at the very least—would not induce “another’s” direct infringement: “Rather, the patentee must prove that the alleged infringer knowingly induced another to commit an infringing act, *i.e.*, the alleged infringer’s sale of its product would actively and knowingly aid and abet another’s direct infringement.” *Id.* at 5. Plaintiffs were well aware.<sup>7</sup>

Plaintiffs’ Infringement Contentions evidence that Plaintiffs not only understood Mylan’s position, they even responded to it. That alone demonstrates that Plaintiffs were on notice of Mylan’s arguments. To be clear, Mylan is not relying on Plaintiffs’ contentions to meet its burden under the Local Rules. *See* Ex. 6 at 1. Mylan met it on its own. And, noting Plaintiffs’ contentions only puts an exclamation point on that as it further demonstrates that Plaintiffs were on notice of Mylan’s position of non-infringement and what Plaintiffs must prove to establish infringement. For example, in *responding to Mylan*, Plaintiffs set forth that it was “Mylan[’s] conten[tion] that it will not induce infringement of the Asserted Claims because it . . . ‘does not cause, urge, encourage, aid, advise, or otherwise induce **any particular party** to practice **any particular claim step** that Mylan, itself, does not practice.’” Ex. 5, Plaintiffs’ Infringement Contentions at 6 (emphasis added). Plaintiffs addressed the purported direct infringers, contending that “Mylan’s Proposed Label is specifically designed to instruct and direct physicians, other healthcare providers, **and/or** patients to administer Mylan’s proposed generic product to patients **who have missed a dose** of its proposed generic product in accordance with the dosing regimens recited in the Asserted Claims.” *Id.* (emphasis added). This undermines Plaintiffs’ newfound “divided infringement” position and is exactly what the parties are addressing—whether two actors are needed (divided infringement) or one (not divided infringement) **under Plaintiffs’ theory of infringement**. That was an issue at the outset of the litigation, and remains one now.

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<sup>6</sup> This alone moots Plaintiffs’ argument that Mylan only “alleged lack of **inducement**, which implicitly assumed the Asserted Claims would be directly infringed.” Mylan never “assumed” direct infringement—Mylan specifically contended there would be no direct infringement which is a **prerequisite** for Plaintiffs to establish induced infringement. *DSU Med. Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1303 (Fed. Cir. 2006).

<sup>7</sup> Plaintiffs’ position phrases factual and legal issues unrelated to the present dispute as if those are uncontested. For example, Plaintiffs state that Mylan “copied the label” of Invega Trinza and posit it almost as a choice of Mylan’s, but Mylan has simply sought FDA approval of a generic version of PP3M and its label is in compliance with FDA regulations and guidelines under the Hatch-Waxman Act. Mylan disputes other aspects of Plaintiffs’ position, but limits this response to the current dispute.



### 3. *Mylan has the Right to Point Out Plaintiffs’ “Absence of Evidence” in a Rebuttal Report.*

To establish induced infringement (Plaintiffs’ sole theory) Plaintiffs must establish direct infringement, and direct infringement requires a single actor meet all claim limitations. Plaintiffs contend that “Mylan’s Proposed Label is specifically designed to instruct and direct physicians, other healthcare providers and/or patients to administer Mylan’s proposed generic product to patients who have missed a dose of its proposed generic product in accordance with the dosing regimens recited in the Asserted Claims.” Ex. 5 at 6. While Plaintiffs’ expert, Dr. Sommi, did not articulate the standard for direct infringement, he did mimic Plaintiffs’ contention, stating that “the infringement inquiry considers whether the proposed label instructs healthcare professionals and/or patients to use the product in accordance with a patent claim.” Ex. 2 at ¶ 60. However, Dr. Sommi also opines that, for example, independent claim 5 requires a missed dose by a patient followed by administering Mylan’s product by only a healthcare professional. *Id.* at ¶¶ 72, 44. Dr. Sommi takes a different opinion from Plaintiffs’ contentions, stating that two actors are required for direct infringement and never once suggesting (as Plaintiffs did in their responsive infringement contentions) that the patient could both miss a dose and then self-administer their next dose after their last dose was given 4-9 months ago.<sup>8</sup> Mylan and its expert have every right to point out and address these differing positions.

A recent decision from this Court is instructive. In *Chiesi USA, Inc. v. Aurobindo Pharma USA, Inc.*, Case No. 19-18756-ZNQ-LHG, 2022 WL 304574, at \*7 (D.N.J. Jan. 9, 2022), the defendant failed to disclose a non-infringement theory in its contentions under the Local Patent Rules. That already separates that case from the one here, since Mylan did disclose its non-infringement theory. Regardless, in deciding the MIL, Judge Quraishi held that while “[t]he Local Patent Rules require an ANDA opponent opposing infringement to speak first by articulating its theories of non-infringement” this Court has been “reluctant to elevate form over substance.” *Id.* The Court continued “[i]t is notable that the ‘affirmative evidence’ [plaintiff] hopes to preclude is testimony from [defendant’s expert] regarding a perceived *absence of evidence*...[t]he Court also recognizes that, as a practical matter, amending to add an evidence-deficiency contention like this one would logically be complicated by [defendant] waiting for [plaintiff] to disclose its evidence.” *Id.* (emphasis in original). Again, Mylan did put Plaintiffs on notice of its non-infringement theory. Plaintiffs responded in their contentions. But even if that were not the case, Mylan is permitted to point out Plaintiffs’ “absence of evidence” in expert discovery. And as a final note, the Court in *Chiesi* also found “there is less prejudice<sup>9</sup> to [plaintiff] given the narrow nature of the non-

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<sup>8</sup> Dr. Sommi also utilizes the fact that more than one actor is required to practice the claimed methods in order to tout the purported benefit of Invega Trinza® over oral medications that **require self-administration**. Ex. 2 at ¶ 23. To utilize the requirement of two actors to tout purported benefits to avoid invalidity, then turnaround and argue that only one actor is required to ensnare Mylan’s proposed generic product is improper.

<sup>9</sup> Plaintiffs have not—because they cannot—set forth any showing that they are prejudiced by Mylan’s timely and adequately disclosed position on non-infringement. *Huertas v. Cap. One Bank, N.A.*, Case No. 17-cv-1891-RMB-AMD, 2019 WL 6254933, at \*4 (D.N.J. Aug. 1, 2019) (“mere conclusory assertions of prejudice will not suffice”). Yet still, Plaintiffs are asking the

infringement theory, and that [plaintiff] had the opportunity to depose [the expert] and can cross-examine him on this issue at trial.” *Id.*

#### **4. *Plaintiffs Delayed Raising this “Issue.”***

Plaintiffs did not raise the issue with the Court until the June 15<sup>th</sup> teleconference. That cuts against Plaintiffs’ concocted timeliness “issue” given that the parties were at an impasse as of May 18<sup>th</sup>. Ex. 6 at 1 (5/18 email from C-V, Lachlan). Knowing that the case is on an expedited schedule and with several upcoming expert depositions, Plaintiffs’ delay is inexcusable. What is more is that the remedy Plaintiffs now seek is considerably different from the one Plaintiffs’ initially raised with Mylan. Mylan’s counsel reached out to Plaintiffs’ counsel to confirm per the scheduling order that reply reports are limited to secondary considerations and that there would be no reply infringement report following ambiguity in prior correspondence when amending the schedule. See Ex. 7 at 2 (4/14 email from S, Lance). Plaintiffs’ response was that they could not “confirm [their] position on reply reports until [they] see [Mylan’s] rebuttal report” and that they “reserve [their] right to pursue a reply if there is a need to do so.” *Id.* at 1 (4/18 email from C-V, Lachlan). Mylan served its rebuttal expert report of Dr. Berger on May 9<sup>th</sup>, and not once have Plaintiffs raised the need for a reply report, instead opting to try for the extreme sanction of entirely striking paragraphs from Dr. Berger’s report. That is the case despite still having the opportunity to depose Dr. Berger (*see Chiesi*, at \*7) and further underscores the impropriety of these litigation tactics.

#### **5. *Plaintiffs First Raised “Claim Construction” During the Parties’ Initial Exchange.***

Plaintiffs never *once* raised an issue of any alleged “newly” advanced claim construction prior to the parties’ agreed upon initial exchange for this Joint Letter. It was never mentioned during the parties’ meet and confer, the Court’s June 15<sup>th</sup> teleconference, nor during the parties’ email communications on this issue. At best, this appears to be an oversight on Plaintiffs’ part during its many conversations with Mylan; at worst, it is evidence of Plaintiffs now trying to manufacture “prejudice” where none exists. Setting that aside though, Plaintiffs are again mistaken because there is no “new claim construction” being proposed by Mylan.<sup>10</sup> The claims

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Court to exclude critical evidence, which would violate the Third Circuit’s directive and impose “an extreme sanction” that may not be “imposed absent a showing of willful deception or ‘flagrant disregard’ of a court order”. *Meyers v. Pennypack Woods Home Ownership Assn.*, 559 F.2d 894, 905 (3d Cir. 1977). None are present here.

<sup>10</sup> Plaintiffs also cite to Mylan’s Invalidity Contentions (Ex. 10), completely out of context, relying on portions regarding Claim 1 (which as noted below were dropped on the eve of rebuttal reports) as Mylan “defining” the patient population. Rather, Mylan’s discussion regarding the preamble of the claims is that it is non-limiting as to “an efficacy requirement” as nothing in the phrase “in need of treatment” requires efficacy. Ex. 10 at 43-4. Mylan’s Invalidity Contentions served concurrently with its Non-Infringement Contentions explicitly state: “The claim language and specification make clear that the focus of the alleged invention is not on a new way of actually treating the underlying condition, but rather the focus is on patient behavior (e.g., a missed dose).” *Id.* at 93-4. Mylan specifically stated that it was applying the plain and ordinary meaning of the claims. *Id.* at 43.

have an ordinary meaning that Plaintiffs acknowledged in prosecuting the patent, in their infringement contentions, and even through their own expert in his infringement report for example, Plaintiffs state that the “Asserted Claims do not refer to the act of missing a dose at all”, but Plaintiffs’ expert disagrees, describing asserted claim 5 based on “when a regularly scheduled dose of PP3M is missed”. Dr. Berger’s report responds directly to Dr. Sommi, but it also specifically states that he was “not asked to offer (nor do[es he] offer) an opinion directed to any claim construction” and that “he has been informed by counsel that unless some other reason exists, *i.e.*, a claim construction order, a claim term should be accorded its plain and ordinary meaning as understood by a POSA when read in context of the specification and prosecution history.” Ex. B at ¶¶ 19-20. Claim construction is not a prerequisite for the Court to weigh and consider the evidence in assessing direct and indirect infringement—both of which Mylan has contested since the earliest stages of litigation.

**6. *Plaintiffs Would Have the Court Mandate a Stricter Standard for Mylan Than Plaintiffs.***

Mylan has litigated this case on the merits since the beginning. If any party has wavered in its positions, it has been Plaintiffs.<sup>11</sup> In the midst of expert discovery, Mylan received a document production of highly relevant and previously requested (during fact discovery), but unproduced, documents just days before Plaintiffs served their rebuttal expert reports relying heavily on such documents. Ex. 8 (5/5 email from Q, Rob). In a baffling narrative, Plaintiffs take the position that while “nothing in the Local Rules or case law requires that every piece of ‘information or data’ to be presented at trial be cited in [Janssen’s] contentions,” somehow the same rules and law do not apply to Mylan. *See* Ex. 6 at 1. Plaintiffs would have the Court rule that even though those “piece[s] of ‘information and data’” were responsive to requests by Mylan not only in RFPs, but during the deposition of Plaintiffs’ Rule 30(b)(6) deponent, Plaintiffs were not under the same disclosure requirements as Mylan. Rather, Plaintiffs take the position that their burden of disclosure should be *less* than that of Mylan. Further, Plaintiffs find no apparent prejudice because “Mylan had (and still has) every opportunity to explore these issues through fact and expert discovery” even though fact discovery closed three (3) months prior in February. *Id.* What is good for Plaintiffs, should be good for Defendant as it goes without saying that Janssen still has “every opportunity to explore” Dr. Berger’s expert report in expert discovery. That is why Mylan believes these “disputes” can be addressed in the normal course of expert discovery. But should the Court disagree, Mylan respectfully submits that Plaintiffs should be held to the same standard and the portions of Plaintiffs’ expert reports relying on late produced documents be struck.

We thank Your Honor for her kind consideration.

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<sup>11</sup> One example is after Mylan and its experts expended significant time defending against arguments regarding claims 1-3 and 15-29, Plaintiffs decided to unilaterally drop those claims just days short of the deadline for rebuttal expert reports. ECF No. 63. Plaintiffs were adamant in their desire to get the claims dismissed “by Monday” (the due date of rebuttal reports) and that if no agreement was reached then they requested that “the parties agree that Janssen will hold its Claim 1 reports in abeyance and put them in only if the parties cannot agree.” Ex. 9, at 1.



Page 11

Highly Confidential

Respectfully,

s/Keith J. Miller

Keith J. Miller

Encl.

cc: All Counsel of Record (w/encl.) (via CM/ECF)

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV, and  
JANSSEN RESEARCH & DEVELOPMENT  
LLC,

*Plaintiffs,*

v.

MYLAN LABORATORIES LIMITED,

*Defendant.*

Civil Action No. 3:20-cv-13103-ZNQ-  
LHG

**OPENING EXPERT REPORT OF ROGER W. SOMMI, JR., PHARM.D.  
REGARDING INFRINGEMENT OF U.S. PATENT NO. 10,143,693**

**HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER**

I, Roger W. Sommi, Jr. declare as follows:

**I. QUALIFICATIONS**

1. I am a Pharmacist with more than 35 years of experience participating in collaborative treatment, teaching, and conducting clinical research of outcomes associated with drug treatment of patients with schizophrenia and other psychiatric disorders. I am board certified in Psychiatric Pharmacy by the Board of Pharmaceutical Specialties and a Fellow of the American College of Clinical Pharmacy. The following is a summary of my background and qualifications. Additional information is provided in my *curriculum vitae*, a copy of which is attached as **Exhibit A** to this report.

2. I am currently Professor of Pharmacy Practice at the University of Missouri-Kansas City (“UMKC”) School of Pharmacy and Professor of Psychiatry at the UMKC School of Medicine.

3. I have my Bachelor of Science degree in Pharmacy from the University of Wisconsin-Madison in 1983, my Doctor of Pharmacy degree from the University of Utah in 1985, and completed a two-year Clinical Sciences Fellowship in Psychiatric Pharmacotherapy at the University of Texas-Austin and Austin State Hospital in 1987.

4. In August 1985, I began my academic career as a Clinical Instructor at the University of Texas-Austin College of Pharmacy, where I worked until August 1987.

5. In October 1987, I joined the faculty at UMKC School of Pharmacy as an Assistant Professor of Pharmacy Practice, a position that I held until September 1993. From September 1993 to September 2003, I served as Associate Professor of Pharmacy Practice. In September 2003, I assumed my current position as Professor of Pharmacy Practice at the school. Since May 2014, I have served as Vice Chair of the Division of Pharmacy Practice and



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Administration and Associate Dean at UMKC School of Pharmacy.

6. In February 1988, I joined the faculty at UMKC School of Medicine as an Assistant Professor of Psychiatry and stayed in that position until September 1993. From September 1993 to September 2003, I served as Associate Professor of Psychiatry. In September 2003, I assumed my current position as Professor of Psychiatry at the school.

7. I have been in practice, seeing patients in an interprofessional treatment team setting (*i.e.*, physicians, resident physicians, nurse practitioners, nurses, psychologists, social workers, and psychiatry technicians), for the past 37 years. My practice has revolved around assessing patients, identifying drug-related problems and making recommendations for treatment. We have multiple learners in the clinical environment as well. I spend significant time annually training psychiatrists, pharmacists, nurse practitioners, physician assistants and other psychiatric professionals on the proper use of psychiatric medicines, including long-acting injectable antipsychotics (“LAIAs”) like Invega Sustenna® and Invega Trinza®. One of the specific areas that I teach is the pharmacokinetics of psychiatric medication generally and LAIAs specifically. I have given multiple national and regional trainings on the use of psychiatric medications generally, and LAIAs in particular.

8. I have been the Research Director of the Psychopharmacy Research and Education Program at UMKC School of Pharmacy and the Center for Behavioral Medicine since August 1988. My clinical research focuses on outcomes associated with drug treatment of patients with schizophrenia and other psychiatric disorders, with a specific focus on the use of antipsychotic medications. I have presented the results of my research, including on outcomes associated with psychiatric drug treatment, at numerous national meetings. I have published dozens of papers in peer-reviewed scientific journals. Many of those papers pertain to

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psychiatric drug treatment. I have received approximately 60 grants and contracts as primary investigator. I have also served as primary investigator of approximately 31 research initiatives. In the course of my career, I have supervised approximately 50 post-doctoral residents and 19 post-doctoral research fellows and supervised the research projects for the postdoctoral program.

9. As a trained psychiatric pharmacist, I am regularly involved with the treatment of psychiatric patients (including patients with schizophrenia). That involves consulting with patients and their prescribers to make choices about drug treatment. Over my career, I estimate I have been personally involved with treatment decisions of several thousand psychiatric patients, many of whom were diagnosed with schizophrenia.

10. By way of example, I have been affiliated with the Southwest Missouri Psychiatric Rehabilitation Center (SWMPRC), an inpatient facility for patients with severe mental illness, for over 20 years. As part of my work with SWMPRC, I convene and chair meetings of the psychiatrists and nurse practitioners at the facility, interview patients, discuss treatment options and medication management, and prepare multi-page assessments and recommendations for the clinical team. I have done and continue to do similar work in other psychiatric settings.

11. I have participated in a number of clinical trials during the course of my career, including as a principal investigator. These include clinical trials of LAIAs, specifically Invega Sustenna®, Zyprexa Relprevv® and Aristada®.

12. I have served as an advisor to multiple pharmaceutical companies on the development of their drugs, including LAIAs. Additionally, I have been invited to be a promotional speaker for many of these companies over the years—including most of the current manufacturers of LAIAs—starting with Haldol-D® and progressing through Risperdal Consta®,

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Invega Sustenna, Abilify Maintena and Aristada.

13. I have been asked by Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, and Janssen Research & Development LLC to provide certain expert opinions in this case. I am being compensated for my time spent working on this case at a rate of \$400 per hour, plus expenses. My compensation is not dependent on the outcome of this case.

**II. SUMMARY OF OPINIONS TO BE EXPRESSED**

14. I have been asked by Janssen's counsel to opine on whether Mylan Laboratories Limited ("Mylan") infringes Claims 1-3, 5-7, and 9-29 of U.S. Patent No. 10,143,693 (the "693 Patent").

15. It is my opinion that the use of Mylan's proposed generic versions of Invega Trinza in accordance with Mylan's proposed prescribing information would infringe Claims 1-3, 5-7, and 9-29 of the 693 Patent.

16. In forming my opinions for this case, I have relied upon the documents cited in this declaration, including those listed in **Exhibit B**. My opinions further applied—and I relied upon in forming my opinions for this case—my education, knowledge, and experience.

17. I will be prepared to testify at trial as to the matters discussed in this report, as well as matters I may discuss in response to any expert report submitted by Mylan. In my testimony, I may provide additional explanations or clarifications of the opinions expressed in my reports, and I may use documents, illustrations, examples, or visual aids that are not included in either report.

**III. BACKGROUND**

**A. The Treatment of Schizophrenia**

18. Schizophrenia is a debilitating illness that affects approximately 1% of the

**From:** [Campbell-Verduyn, Lachlan \(x2295\)](#)  
**To:** [Soderstrom, Lance A.](#); [Schurr, Jillian M.](#); [Quirk, Rob \(x2204\)](#); [Mukerjee, Deepto R.](#); [Malik, Jitty](#); [El-Khoury, Dawn S.](#); [Arnie Calmann](#); [Jeffrey Soos](#); [Katherine A. Escanlar](#)  
**Cc:** ["Keith Miller"](#); [jquinn@rwmlegal.com](#); [Michael Gesualdo](#); [\\_cg Trinza](#)  
**Subject:** RE: Janssen Pharmaceuticals Inc. et al. v. Mylan Laboratories Ltd. (No. 3:20-cv-13103)  
**Date:** Monday, April 18, 2022 9:57:44 AM

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***EXTERNAL EMAIL – EXERCISE CAUTION***

Lance,

We can't confirm our position on reply reports until we see your rebuttal report. We reserve our right to pursue a reply if there is a need to do so.

Thank you,

Lachlan

---

**From:** Soderstrom, Lance A. <lance.soderstrom@katten.com>  
**Sent:** Monday, April 18, 2022 10:21 AM  
**To:** Campbell-Verduyn, Lachlan (x2295) <lcampbellverduyn@pbwt.com>; Schurr, Jillian M. <jillian.schurr@katten.com>; Quirk, Rob (x2204) <rquirk@pbwt.com>; Mukerjee, Deepto R. <deepto.mukerjee@katten.com>; Malik, Jitty <jitty.malik@katten.com>; El-Khoury, Dawn S. <dawn.el-khoury@katten.com>; Arnie Calmann <ACalmann@saiber.com>; Jeffrey Soos <JSoos@saiber.com>; Katherine A. Escanlar <KEscanlar@saiber.com>  
**Cc:** 'Keith Miller' <KMiller@rwmlegal.com>; jquinn@rwmlegal.com; Michael Gesualdo <MGesualdo@rwmlegal.com>; \_cg Trinza <Trinza@pbwt.com>  
**Subject:** RE: Janssen Pharmaceuticals Inc. et al. v. Mylan Laboratories Ltd. (No. 3:20-cv-13103)

**Caution: External Email!**

Lachlan –

Sure. My email of March 3<sup>rd</sup> to Andrew may have unnecessarily injected ambiguity as we think the scheduling order is clear. And I just want to make sure there is no “surprise” down the road by pointing to my March 3<sup>rd</sup> email. Please confirm.

Thank you,

**Lance A. Soderstrom**  
Partner & National Co-Chair, Patent Litigation

**Katten**

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**From:** Campbell-Verduyn, Lachlan (x2295) <[lcampbellverduyn@pbwt.com](mailto:lcampbellverduyn@pbwt.com)>  
**Sent:** Monday, April 18, 2022 10:17 AM  
**To:** Soderstrom, Lance A. <[lance.soderstrom@katten.com](mailto:lance.soderstrom@katten.com)>; Schurr, Jillian M. <[jillian.schurr@katten.com](mailto:jillian.schurr@katten.com)>; Quirk, Rob (x2204) <[rquirk@pbwt.com](mailto:rquirk@pbwt.com)>; Mukerjee, Deepro R. <[deepro.mukerjee@katten.com](mailto:deepro.mukerjee@katten.com)>; Malik, Jitty <[jitty.malik@katten.com](mailto:jitty.malik@katten.com)>; El-Khoury, Dawn S. <[dawn.el-khoury@katten.com](mailto:dawn.el-khoury@katten.com)>; Arnie Calmann <[ACalmann@saiber.com](mailto:ACalmann@saiber.com)>; Jeffrey Soos <[JSoos@saiber.com](mailto:JSoos@saiber.com)>; Katherine A. Escanlar <[KEscanlar@saiber.com](mailto:KEscanlar@saiber.com)>  
**Cc:** 'Keith Miller' <[KMiller@rwmlegal.com](mailto:KMiller@rwmlegal.com)>; [jquinn@rwmlegal.com](mailto:jquinn@rwmlegal.com); Michael Gesualdo <[MGesualdo@rwmlegal.com](mailto:MGesualdo@rwmlegal.com)>; \_cg Trinza <[Trinza@pbwt.com](mailto:Trinza@pbwt.com)>  
**Subject:** RE: Janssen Pharmaceuticals Inc. et al. v. Mylan Laboratories Ltd. (No. 3:20-cv-13103)

*EXTERNAL EMAIL – EXERCISE CAUTION*

Lance,

Can you please explain why you are seeking our position on this issue at this time?

Thank you,

Lachlan

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**From:** Soderstrom, Lance A. <[lance.soderstrom@katten.com](mailto:lance.soderstrom@katten.com)>  
**Sent:** Thursday, April 14, 2022 11:04 AM  
**To:** Campbell-Verduyn, Lachlan (x2295) <[lcampbellverduyn@pbwt.com](mailto:lcampbellverduyn@pbwt.com)>; Schurr, Jillian M. <[jillian.schurr@katten.com](mailto:jillian.schurr@katten.com)>; Quirk, Rob (x2204) <[rquirk@pbwt.com](mailto:rquirk@pbwt.com)>; Mukerjee, Deepro R. <[deepro.mukerjee@katten.com](mailto:deepro.mukerjee@katten.com)>; Malik, Jitty <[jitty.malik@katten.com](mailto:jitty.malik@katten.com)>; El-Khoury, Dawn S. <[dawn.el-khoury@katten.com](mailto:dawn.el-khoury@katten.com)>; Arnie Calmann <[ACalmann@saiber.com](mailto:ACalmann@saiber.com)>; Jeffrey Soos <[JSoos@saiber.com](mailto:JSoos@saiber.com)>; Katherine A. Escanlar <[KEscanlar@saiber.com](mailto:KEscanlar@saiber.com)>  
**Cc:** 'Keith Miller' <[KMiller@rwmlegal.com](mailto:KMiller@rwmlegal.com)>; [jquinn@rwmlegal.com](mailto:jquinn@rwmlegal.com); Michael Gesualdo <[MGesualdo@rwmlegal.com](mailto:MGesualdo@rwmlegal.com)>; \_cg Trinza <[Trinza@pbwt.com](mailto:Trinza@pbwt.com)>  
**Subject:** RE: Janssen Pharmaceuticals Inc. et al. v. Mylan Laboratories Ltd. (No. 3:20-cv-13103)

**Caution: External Email!**

Lachlan –

We are in receipt of your letter but had a closing argument yesterday in a separate matter, so have not had the chance to respond. That said, we expect to provide our response early next week. Also, while I think it's clear from the Amended Scheduling Order Extending Deadlines for Exchange of Expert Reports, I want to make sure that all parties understand the only reply reports being submitted on June 3<sup>rd</sup> will be from us (i.e., there will not be a reply infringement report). Please let us know by Monday if you disagree.

Thanks,

# Exhibit A



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Attorneys for Defendant  
Mylan Laboratories Limited

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV, and  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

Plaintiffs,

v.

MYLAN LABORATORIES LIMITED,

Defendant.

Civil Action No. 3:20-cv-13103-BRM-LHG

**CONFIDENTIAL**

**DEFENDANT MYLAN LABORATORIES LIMITED'S INITIAL  
NON-INFRINGEMENT CONTENTIONS**

Pursuant to Local Patent Rules (L. Pat. R.) 3.3 and 3.6, and the Scheduling Order (ECF No. 30), Defendant Mylan Laboratories Ltd. (“Mylan”) hereby submits the following Non-Infringement Contentions to Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV and Janssen Research & Development, LLC (collectively, “Plaintiffs”) concerning U.S. Patent No. 10,143,693 (“the ’693 patent”). In their Disclosures of Asserted Claims, Plaintiffs state that they are asserting claims 1-3, 5-7 and 9-29 of the ’693 patent.

Mylan reserves the right to supplement, amend, or otherwise modify these contentions as discovery proceeds, including based on information obtained through fact and expert discovery, or upon further investigation. Mylan further reserves the right to supplement, amend, or otherwise modify these contentions in accordance with any modification to the Scheduling Order entered by the Court; in response to any supplements or amendments to Plaintiffs’ Disclosure of Asserted Claims; in response to Plaintiffs’ forthcoming Infringement Contentions and Response to Invalidity Contentions; or in response to any claim construction ruling by the Court regarding the ’693 patent; or after any decision by this Court or the United States Court of Appeals for the Federal Circuit that bears on the construction or validity of the ’693 patent. In addition, to the extent that Plaintiffs advance a claim construction position different than Mylan’s current understanding of a claim term (or Plaintiffs’ positions concerning such claim term) and/or after the Court construes the claims as a matter of law, Mylan expressly reserves the right to modify these Non-Infringement Invalidity Contentions. Mylan therefore reserves the right to supplement, amend, or otherwise modify these contentions in accordance with the Local Patent Rules or any other applicable Rules or by order of this Court or as appropriate. Mylan also provides these disclosures without waiving any claim of privilege or work-product immunity.

These contentions are made pursuant to Federal Rule of Evidence 502. To the extent these contentions contain any information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity or any other applicable privilege or immunity, such disclosure is inadvertent and does not, nor is it intended to, constitute a waiver of any such privilege or immunity. The information set forth in these contentions is provided without waiving: (1) the right to object to the use of any statement for any purpose, in this action or any other, on the grounds of privilege, relevance, materiality, or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement, or clarify any of the statements provided below at any time.

These contentions should not be taken as an indication of Mylan's position with regard to the proper construction of any claim term. Rather, Mylan has made reasonable assumptions, to the extent necessary and appropriate, as to the meaning of claim terms for the purpose of these contentions only and have used those meanings to prepare these contentions. To the extent that Mylan determines that a different meaning is appropriate for any claim term, they will assert that meaning in connection with the claim construction proceedings, and Mylan reserves the right to amend these contentions as a result of the *Markman* hearing and/or decision, or any other subsequent clarification or alteration of the meaning of claim terms.

As discussed in more detail below, at this early stage of the litigation, Mylan submits the following non-infringement contentions:

- In light of prior art and other documents (produced as Bates numbers (MYL-PP3M055716-6063), and as set forth in detail in Mylan's Initial Invalidity Contentions Pursuant to L. Pat. R. 3.3 and 3.6, served concurrently herewith, each

of the Asserted Claims is invalid. Accordingly, because the Asserted Claims are invalid, Mylan's proposed product, as described in ANDA 212290 ("Mylan's ANDA Product") cannot infringe any of the Asserted Claims.

- Moreover, Mylan will not directly or indirectly infringe the Asserted Claims, either literally or under the doctrine of equivalents. As discussed in detail below, the Asserted Claims recite "administering" and Mylan does not perform the requisite administering step. Because Mylan would never administer any treatment, Mylan cannot directly infringe the Asserted Claims. Mylan does not cause, urge, encourage, aid, advise, or otherwise induce any particular party to practice any particular claim step that Mylan, itself, does not practice, *i.e.*, treating a subject having a disorder. Accordingly, Mylan cannot be liable for direct or induced infringement of any of the Asserted Claims.

## **I. WRITTEN BASIS UNDER L. PAT. R. 3.6(e)**

### **A. An Invalid Claim Cannot Be Infringed**

It is axiomatic that an invalid claim cannot be infringed. As set forth in detail in Mylan's Initial Invalidity Contentions Pursuant L. Pat. R. 3.6(c), served concurrently herewith, each of the Asserted Claims is invalid. Because the Asserted Claims are invalid, Mylan cannot infringe any of the Asserted Claims.

### **B. Mylan Will Not Infringe the Asserted Claims of the '693 Patent**

#### **1. Mylan Will Not Directly Infringe the Asserted Claims**

Direct infringement requires that a single party's activities meet all the limitations as claimed. To infringe a claim comprising a series of steps, "a person must have practiced all steps" of the claim. *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1317 (Fed. Cir. 2009). Here, the Asserted Claims require administering the claimed composition.

Mylan does not, and would never, directly administer Mylan's ANDA Product to a patient. Therefore, Mylan does not perform the requisite administering step of the Asserted Claims. Accordingly, Mylan will not directly infringe any of the Asserted Claims.

**2. Mylan Will Not Indirectly Infringe the Asserted Claims under 35 U.S.C. § 271(b)**

Mylan will not induce infringement of the Asserted Claims under 35 U.S.C. § 271(b). “[I]nduced infringement under § 271(b) requires knowledge that the induced acts constitute patent infringement.” *Glob.-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 766, (2011). Moreover, induced infringement requires that the accused infringer engage in “culpable conduct, directed to encouraging another’s infringement, not merely that the inducer had knowledge of the direct infringer’s activities.” *DSU Med Corp. v. JMS Co., Ltd*, 471 F.3d. 1293, 1306 (Fed Cir. 2006) (*en banc*) (citing *Metro-Goldwyn-Mayer Studios Inc. v. Gorkster, Ltd.*, 545 U.S. 913, 936-37 (2005)); *see also Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003) (“mere knowledge of possible infringement by others does not amount to inducement”).

The Federal Circuit has held that “the intent requirement for inducement requires more than just intent to cause the acts that produce direct infringement.” *DSU*, 471 F.3d at 1306. Rather, the patentee must prove that the alleged infringer knowingly induced another to commit an infringing act, i.e., the alleged infringer’s sale of its product would actively and knowingly aid and abet another’s direct infringement. *See id.* at 1305; *see also MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp.*, 420 F.3d 1369, 1378 (Fed. Cir. 2005); *ACCO Brands, Inc. v. ABA Locks Mfg. Co., Ltd.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007).

Here, Mylan does not have control over whether a subject is actually provided, treated, and/or administered the composition. Moreover, Mylan does not cause, urge, encourage, aid, advise, or otherwise induce any particular party to practice any particular claim step that Mylan,

itself, does not practice, *i.e.*, administering a claimed composition. Therefore, Mylan cannot infringe such non-practiced limitations in the Asserted Claims.

Similarly, Mylan's manufacture, use, sale, offer to sell, or importation into the United States of Mylan's ANDA Product will not induce infringement of the Asserted Claims because Mylan lacks the specific intent necessary to induce infringement of the claims. *DSU*, 471 F.3d at 1306 (inducement of infringement requires specific intent to cause direct infringement). Mylan does not and will not directly instruct physicians or anyone else to practice, much less infringe, the Asserted Claims. Thus, Mylan does not have the requisite specific intent required to induce infringement.

Additionally, Mylan will not infringe claims 27-29 because Mylan's Label for its ANDA Product will not instruct physicians or anyone else to administer "intramuscularly in the deltoid or gluteal muscle of said patient a fourth reinitiation maintenance dose of . . . PP1M."

## **II. CLAIM CHARTS UNDER L. PAT. R. 3.6(e)**

A chart relevant to the '693 patent, setting forth the information required under Local Patent Rule 3.6(e), is attached as Exhibit A. Mylan reserves the right to modify, supplement, or amend this disclosure based on any claim construction ordered by the Court, further discovery, or in view of Plaintiffs' contentions.

## **III. CONCLUSION**

For at least the reasons set forth above, and in light of at least the references discussed herein, Mylan asserts that the Asserted Claims are not infringed by Mylan's ANDA Product. Mylan reserves the right to supplement and/or revise these contentions as necessary and appropriate, including as provided under the Local Patent Rules or any other applicable Rules or order of the Court.

Date: May 26, 2021

/s/ Guylaine Hache

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Attorneys for Defendant  
Mylan Laboratories Limited



**Exhibit A**

	<b>Text of Claim</b>	<b>Reasons for Non-Infringement</b>
1	<p>A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with a 3-month injectable paliperidone palmitate depot (PP3M), wherein said patient had been last administered a PP3M injection more than 9 months ago, and the next scheduled maintenance dose of the PP3M should be administered to said patient, comprising:</p> <p>(1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of 150 mg eq. of monthly injectable paliperidone palmitate depot (PP1M);</p> <p>(2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of 100 mg eq. of PP1M on about the 4th day to about the 12th day after administering said first reinitiation loading dose;</p> <p>(3) administering intramuscularly in the deltoid or gluteal muscle of said patient a first reinitiation maintenance dose of 50 mg eq. to about 150 mg eq. of PP1M on about the 23th day to about the 37th day after administering said second reinitiation loading dose;</p> <p>(4) administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering of the first reinitiation maintenance dose;</p> <p>(5) administering intramuscularly in the deltoid or gluteal muscle of said patient a</p>	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan cannot be held liable for direct infringement of this claim. This claim pertains to a dosing regimen comprising the step of administering the claimed composition. Because Mylan will not directly administer its ANDA Product to a patient, Mylan cannot directly infringe this claim.</p> <p>Moreover, Mylan cannot be held liable for indirect or induced infringement. Mylan does not cause, urge, encourage, aid, advise, or otherwise induce any particular party to practice any particular claim step that Mylan, itself, does not practice, <i>i.e.</i>, administering the claimed composition. Mylan does not and will not directly instruct physicians or anyone else to practice, much less infringe, the claimed dosing regimen. Therefore, Mylan cannot infringe such non-practiced limitations. Thus, Mylan does not have the requisite specific intent required to induce infringement.</p>

	<p>third reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering of the second reinitiation maintenance dose; and</p> <p>(6) administering intramuscularly in the deltoid or gluteal muscle of said patient from about 175 mg eq. to about 525 mg eq. of PP3M on about the 23rd day to about the 37th day after administering of the last reinitiation maintenance dose of monthly injectable paliperidone palmitate.</p>	
2	The method of claim 1, wherein said patient is in need of treatment for psychosis.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
3	The method of claim 1, wherein said patient is in need of treatment for schizophrenia.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
5	<p>A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with PP3M, wherein said patient had been last administered a PP3M injection 4 to 9 months ago and the next scheduled maintenance dose of PP3M should be administered to said patient, comprising:</p> <p>(1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M;</p>	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan cannot be held liable for direct infringement of this claim. This claim pertains to a dosing regimen comprising the step of administering the claimed composition. Because Mylan will not directly administer its ANDA Product to a patient, Mylan cannot directly infringe this claim.</p>

	<p>(2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose; and</p> <p>(3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose</p> <table border="1"> <thead> <tr> <th>Missed Dose of PP3M</th><th>Reinitiation Doses of PP1M</th><th>Reinitiation Doses of PP3M</th></tr> </thead> <tbody> <tr> <td>175 mg eq.</td><td>50 mg eq.</td><td>175 mg eq.</td></tr> <tr> <td>263 mg eq.</td><td>75 mg eq.</td><td>263 mg eq.</td></tr> <tr> <td>350 mg eq.</td><td>100 mg eq.</td><td>350 mg eq.</td></tr> <tr> <td>525 mg eq.</td><td>100 mg eq.</td><td>525 mg eq.</td></tr> </tbody> </table>	Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M	175 mg eq.	50 mg eq.	175 mg eq.	263 mg eq.	75 mg eq.	263 mg eq.	350 mg eq.	100 mg eq.	350 mg eq.	525 mg eq.	100 mg eq.	525 mg eq.	<p>Moreover, Mylan cannot be held liable for indirect or induced infringement. Mylan does not cause, urge, encourage, aid, advise, or otherwise induce any particular party to practice any particular claim step that Mylan, itself, does not practice, <i>i.e.</i>, administering the claimed composition. Mylan does not and will not directly instruct physicians or anyone else to practice, much less infringe, the claimed dosing regimen. Therefore, Mylan cannot infringe such non-practiced limitations. Thus, Mylan does not have the requisite specific intent required to induce infringement.</p>
Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M															
175 mg eq.	50 mg eq.	175 mg eq.															
263 mg eq.	75 mg eq.	263 mg eq.															
350 mg eq.	100 mg eq.	350 mg eq.															
525 mg eq.	100 mg eq.	525 mg eq.															
6	<p>The method of claim 5, wherein said patient is in need of treatment for psychosis.</p>	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 5.</p>															
7	<p>The method of claim 5, wherein said patient is in need of treatment for schizophrenia.</p>	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 5.</p>															
9	<p>The method of claim 5 wherein the second reinitiation dose of PP1M is administered about 7 days after administering said first reinitiation loading dose of PP1M.</p>	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p>															

		Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 5.
10	The method of claim 9 wherein the second reinitiation dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 5.</p>
11	The method of claim 5 wherein the reinitiation dose of PP3M is administered about 30 days after administering said second reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 5.</p>
12	The method of claim 11 wherein the reinitiation dose of PP3M is administered 30 days after administering said second reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 5.</p>
13	The method of claim 5 wherein the reinitiation dose of PP3M is administered about a month after administering said second reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 5.</p>
14	The method of claim 11 wherein the reinitiation dose of PP3M is administered a month after administering said second reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p>

		Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 5.
15	The method of claim 1 wherein the second reinitiation loading dose of PP1M is administered about 7 days after administering said first reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
16	The method of claim 15 wherein the second reinitiation loading dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
17	The method of claim 1 wherein the first reinitiation maintenance dose of PP1M is administered about 30 days after administering said second reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
18	The method of claim 1 wherein the first reinitiation maintenance dose of PP1M is administered 30 days after administering said second reinitiation loading dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
19	The method of claim 1 wherein the second reinitiation maintenance of PP1M is administered about 30 days after administering said first reinitiation maintenance dose of PP1M.	This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.

		Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.
20	The method of claim 1 wherein the second reinitiation maintenance of PP1M is administered 30 days after administering said first reinitiation maintenance dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
21	The method of claim 1 wherein the third reinitiation maintenance of PP1M is administered about 30 days after administering said second reinitiation maintenance dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
22	The method of claim 1 wherein the third reinitiation maintenance of PP1M is administered 30 days after administering said second reinitiation maintenance dose of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
23	The method of claim 1 wherein PP3M is administered about 30 days after administering said last reinitiation maintenance of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
24	The method of claim 1 wherein PP3M is administered about 30 days after administering said last reinitiation maintenance of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p>

		Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.
25	The method of claim 1 wherein PP3M is administered about a month after administering said last reinitiation maintenance of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
26	The method of claim 1 wherein PP3M is administered a month after administering said last reinitiation maintenance of PP1M.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1.</p>
27	The method of claim 1 further comprising administering intramuscularly in the deltoid or gluteal muscle of said patient a fourth reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering the third reinitiation maintenance dose.	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1. Mylan will further not infringe this claim because Mylan's Label for its ANDA Product will not instruct physicians or anyone else to administer "intramuscularly in the deltoid or gluteal muscle of said patient a fourth reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering the third reinitiation maintenance dose."</p>
28	The method of claim 27 wherein said fourth reinitiation maintenance of PP1M is administered about 30 days after administering said third reinitiation maintenance dose of PP1M.	This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.



		<p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1. Mylan will further not infringe this claim because Mylan's Label for its ANDA Product will not instruct physicians or anyone else to administer "intramuscularly in the deltoid or gluteal muscle of said patient a fourth reinitiation maintenance of PP1M is administered about 30 days after administering said third reinitiation maintenance dose of PP1M."</p>
29	<p>The method of claim 28 wherein said fourth reinitiation maintenance of PP1M is administered 30 days after administering said third reinitiation maintenance dose of PP1M.</p>	<p>This claim is invalid under 35 U.S.C. §§ 102, 103, 112 and 101. Accordingly, because this claim is invalid, Mylan cannot infringe this claim.</p> <p>Additionally, Mylan will not directly or indirectly infringe this claim for the same reasons as claim 1. Mylan will further not infringe this claim because Mylan's Label for its ANDA Product will not instruct physicians or anyone else to administer "intramuscularly in the deltoid or gluteal muscle of said patient a fourth reinitiation maintenance of PP1M is administered 30 days after administering said third reinitiation maintenance dose of PP1M."</p>

**CERTIFICATE OF SERVICE**

I hereby certify that on May 26, 2021, I served via electronic mail on counsel of record a true and correct copy of the foregoing.

By: /s/ Guylaine Hache  
Guylaine Hache

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

CHAMBERS OF  
**LOIS H. GOODMAN**  
UNITED STATES MAGISTRATE JUDGE

CLARKSON S. FISHER U.S. COURTHOUSE  
402 EAST STATE STREET  
ROOM 7050  
TRENTON, NJ 08608  
609-989-2114

August 4, 2022

**LETTER ORDER**

**Re: JANSSEN PHARMACEUTICALS, INC., et al. v. MYLAN  
LABORATORIES LTD.  
Civil Action No. 20-13103 (GC) (LHG)**

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Dear Counsel:

Presently before the Court is the parties' joint letter concerning Defendant Mylan Laboratories Ltd.'s ("Mylan") rebuttal expert report ("Joint Letter") [Docket Entry No. 72]. Specifically, Plaintiffs Janssen Pharmaceuticals, Inc., Janssen Pharmaceuticals NV, and Janssen Research & Development, LLC (collectively, "Janssen") ask the Court to strike the opinions of Mylan's rebuttal expert, Dr. Steven Berger, M.D., as to divided infringement.

Janssen argues that Mylan failed to disclose this theory in Mylan's non-infringement contentions and that Janssen should not be forced to prepare for trial—currently scheduled for October 3, 2022—on this newly disclosed theory. Joint Letter at 3–5. Janssen would therefore suffer prejudice if the Court does not grant the relief sought. Joint Letter at 3–4. Mylan disputes Janssen's characterizations and maintains, *inter alia*, that Mylan adequately provided notice of its non-infringement positions to Janssen and that Janssen is now attempting to allege prejudice where none exists. Joint Letter at 5–9. The Court should deny Janssen's request, which Mylan asserts is an unwarranted *motion in limine* disguised as a discovery issue. Joint Letter at 5–7.

After reviewing the Joint Letter and considering the parties' arguments, this Court finds that the issue relates to trial admissibility, not discovery. Specifically, Janssen seeks the exclusion of this theory from Mylan's case at trial. Therefore, the undersigned finds that this issue would be more appropriately presented as a *motion in limine*. This is particularly so, given the timing of the letter request and the proximity of trial.

Case 3:20-cv-13103-GC-LHG Document 78 Filed 08/04/22 Page 2 of 2 PageID: 1383

Accordingly, it is **ORDERED** that Janssen's request to strike portions of Dr. Berger's rebuttal report is denied without prejudice at this time. Janssen may file the appropriate *motion in limine* in accordance with the timeline as set by the Court for such motions.

**IT IS SO ORDERED.**

A handwritten signature in black ink, appearing to read "Lois H. Goodman", written over a horizontal line.

**LOIS H. GOODMAN**  
**United States Magistrate Judge**

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
and JANSSEN RESEARCH &  
DEVELOPMENT, LLC,

Plaintiffs,

v.

MYLAN LABORATORIES LIMITED,  
Defendant.

**Civil Action No. 3:20-cv-13103  
(GC) (LHG)**

**FILED UNDER SEAL**

**PLAINTIFFS' MOTION *IN LIMINE*  
TO EXCLUDE MYLAN'S DIVIDED INFRINGEMENT DEFENSE**

## **TABLE OF CONTENTS**

	<b><u>Page</u></b>
Table of Authorities .....	ii
INTRODUCTION .....	1
I. BACKGROUND .....	3
II. DIVIDED INFRINGEMENT IS NOT APPLICABLE TO THE 693 PATENT .....	5
A. A Patient “Missing a Dose” Is Not a Step In the Dosing Regimen Claimed in the 693 Patent.....	6
1. The Structure and Grammar of the Asserted Claims Make Clear that “Missing a Dose” Is Not a Claim Step.....	6
2. The Purpose of the Asserted Claims Confirms That the Plain and Ordinary Meaning Does Not Include Missing a Dose as a Claim Step.....	10
3. Construing “Missing a Dose” to be a Claim Step Leads to Absurd Results .....	10
B. All of the Steps of the Claimed Method are Performed By a Single Actor.....	14
III. MYLAN FAILED TO TIMELY DISCLOSE ITS DIVIDED INFRINGEMENT ARGUMENT.....	14
A. Mylan’s Divided Infringement Theory Was Not Disclosed in Its Non-Infringement Contentions or During Claim Construction .....	15
B. The Court Should Strike Mylan’s Divided Infringement Defense .....	17

**TABLE OF AUTHORITIES****Page(s)****Cases**

<i>AMAG Pharms., Inc. v. Sandoz, Inc.</i> , No. 16-cv-1508, 2017 WL 3076974 (D.N.J. July 19, 2017).....	7, 9, 10
<i>Celgene Corp. v. Hetero Labs</i> , No. 17-cv-3387, 2021 WL 3701700 (D.N.J. June 15, 2021) .....	17, 18, 19
<i>Chiesi United States v. Aurobindo Pharma United States</i> , No. 19-cv-18756, 2022 WL 304574 20102 (D.N.J. Jan. 9, 2022) .....	17, 18
<i>Core Wireless Licensing S.A.R.L. v. Apple, Inc.</i> No. 15-cv-5008, 2016 WL 6427850 (N.D. Cal. Oct. 31, 2016).....	7, 8, 9, 10
<i>Cytologix Corp. v. Ventana Med. Sys.</i> , 424 F.3d 1168 (Fed. Cir. 2005) .....	14
<i>Eli Lilly &amp; Co. v. Teva Parenteral Meds., Inc.</i> , 845 F.3d 1357 (Fed. Cir. 2017) .....	5
<i>Limelight Networks, Inc. v. Akamai Techs., Inc.</i> , 572 U.S. 915 (2014).....	6
<i>Merck Sharp &amp; Dohme Corp. v. Sandoz, Inc.</i> , No. 12-cv-3289, 2014 WL 997532 (D.N.J. Jan. 6, 2014) .....	17
<i>Microprocessor Enhancement Corp. v. Texas Instruments, Inc.</i> , 520 F.3d 1367 (Fed. Cir. 2008) .....	7
<i>Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.</i> , 282 F. Supp. 3d 793 (D. Del. 2017).....	5, 8, 9, 10
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005) (en banc) .....	6
<i>Trimed, Inc. v. Arthrex, Inc.</i> , No. 18-cv-666, 2021 WL 1174532 (D. Del. Mar. 29, 2021).....	14



**TABLE OF AUTHORITIES**  
**(continued)**

	<b><u>Page (s)</u></b>
<b>Other Authorities</b>	
Fed. R. Evid. 402 .....	6, 15
Fed. R. Evid. 403 .....	6, 15
Local Patent Rule 3.6 .....	15
Local Patent Rule 3.7 .....	19

## **INTRODUCTION**

This action arises out of Mylan’s applications to the FDA to market generic versions of Janssen’s Invega Trinza®, a long-acting paliperidone palmitate antipsychotic medication that is administered every three months (also called “PP3M”). Janssen alleges that Mylan infringes Claims 5-7 and 9-14 (the “Asserted Claims”) of its U.S. Patent No. 10,143,693 (“693 Patent”), which cover dosing regimens that allow patients who have missed a dose of PP3M to return to treatment. Both Janssen’s label for Invega Trinza® and Mylan’s label for its proposed generic include instructions for the claimed missed dose dosing regimen.

Mylan does not dispute the basic facts of infringement: that it copied Janssen’s label for its proposed generic product (including the claimed dosing regimen) and that following the missed dose dosing regimens on Mylan’s proposed label would infringe the Asserted Claims. Instead, Mylan asserts that, despite copying Janssen’s patented dosing regimen, it does not infringe the Asserted Claims under a strained theory of “divided infringement.” Under this theory, Mylan argues that the steps of the claimed dosing regimens include the “act” of missing a dose, which can only be performed by the patient. As a result, the theory goes, there is no single actor who practices the claimed method of treatment as required for infringement, because it is a doctor who administers the claimed dosing regimen but a patient who missed the dose.

Mylan's divided infringement theory is both meritless and untimely. Janssen therefore moves for an order excluding any testimony on this late-disclosed theory.

Divided infringement is inapplicable to the Asserted Claims. The plain language of the claims simply does not include the "act" of missing a dose. Rather, the preamble of the Asserted Claims defines the condition of the patient (having missed a scheduled dose of PP3M) who receives the claimed method of treatment. Thereafter, the Asserted Claims set out three steps of the claimed regimens. Mylan's theory transforms a patient's *condition* requiring treatment into an active step of the treatment. Mylan's interpretation of method of treatment claims is entirely unsupported by law, contrary to the plain language of the claims, and would make it virtually impossible for any method of treatment claim to be infringed. The Court should preclude Mylan from introducing testimony on this baseless and futile theory, which will only waste the Court's, the parties', and the witnesses' time.

Furthermore, Mylan's divided infringement theory was not disclosed in a timely fashion. It was not disclosed in Mylan's infringement contentions, as expressly required by the local patent rules, or during the time scheduled for raising claim construction disputes. Mylan introduced this new theory for the first time in its *rebuttal* expert report on infringement, without seeking leave to amend

its contentions, in violation of this Court's local rules. Courts in this district regularly preclude testimony on this basis alone and the Court should do the same here.

## **I. BACKGROUND**

This is a Hatch-Waxman case involving Janssen's 693 Patent, listed in the Orange Book for Janssen's Invega Trinza® product. Invega Trinza is a long-acting injectable paliperidone palmitate antipsychotic medication that can be administered once every three months, providing sustained treatment for patients while reducing opportunities for non-adherence. Nevertheless, PP3M patients do miss their regularly scheduled dose from time to time. The 693 Patent solves the problem of how to return such patients to PP3M treatment. The Asserted Claims recite the steps to be taken to reinitiate a psychiatric patient treated with PP3M, whose last dose of PP3M was 4-9 months ago. Those steps are administering to these patients two specific doses of one-month paliperidone palmitate ("PP1M") and PP3M, at specific time intervals, by injection in specific locations, then resuming treatment with PP3M. These same steps are set forth in the missed dose instructions in the Invega Trinza prescribing information.

Mylan's proposed prescribing information copies the Invega Trinza missed dose instructions nearly verbatim. Janssen alleges that, by including such instructions in its label, Mylan has induced infringement of the Asserted Claims.

When Mylan provided its non-infringement contentions over a year ago, it did not dispute that healthcare providers (“HCPs”) would infringe the Asserted Claims by administering PP3M according to Mylan’s proposed label. Instead, Mylan contended that **Mylan itself** would not directly infringe (because **Mylan itself** does not administer any drug), and that Mylan would not induce infringement (despite its copied label instructions), because the label would not cause HCPs to administer the drug according to the missed dose regimen. *See* Ex. 1 at 4-6 (Mylan’s May 26, 2021 Non-Infringement Contentions). In its contentions, Mylan never disputed (as it does now) that a HCP following its proposed label would directly infringe the Asserted Claims.

Mylan has since introduced a new theory of non-infringement in the rebuttal infringement report of its expert, Dr. Steven Berger. Dr. Berger opined that a HCP following the label would not directly infringe because infringement is “divided” between the HCP who administers the dosing regimen and the patient who misses a dose. Mylan’s theory is premised on a previously undisclosed construction of the claims that improperly reads the condition for treatment into the steps for treatment. Janssen promptly raised the untimeliness of the theory (and its lack of merit) first with Mylan and then with Judge Goodman, who ordered submission of a joint letter, attached here as Exhibit 2. Judge Goodman denied Janssen’s request without prejudice to renewal as a motion *in limine*. Dkt. 78 at 1.

## II. DIVIDED INFRINGEMENT IS NOT APPLICABLE TO THE 693 PATENT

“Divided infringement” refers to the situation where “no single actor performs all *steps* of a method claim.” *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1364 (Fed. Cir. 2017) (emphasis added). “Divided infringement” is a defense to direct infringement. But if a single actor *does* perform all of the steps of a method claim, then there is no divided infringement. Applied to the Hatch-Waxman context, that means that where the label for the proposed ANDA product directs a single actor to perform all steps of a claimed method of treatment, infringement is not divided. In such a case, the single actor infringes directly and any party that induces that infringement by instructing that actor to perform the claimed method is liable for induced infringement. *See Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.*, 282 F. Supp. 3d 793, 811-12, 818 (D. Del. 2017) (rejecting argument that divided infringement applied to method of treatment claim), *aff’d in part, rev’d in part sub nom. Nalproprion Pharms., Inc., v. Actavis Labs. FL, Inc.*, 934 F.3d 1344 (Fed Cir. 2019).

Here, the only *steps* of the Asserted Claims are the steps of administering PP1M or PP3M; they do not include the step of a patient missing a dose. It is undisputed that a single actor (the HCP) performs all administering steps. Mylan’s divided infringement theory reads into the Asserted Claims the “act of missing a dose,” contrary to the express language of the claim and its plain and ordinary

meaning. Mylan’s divided infringement argument and associated expert testimony should therefore be excluded as irrelevant under Federal Rule of Evidence 402 and as a waste of time and source of undue delay under Rule 403.

**A. A Patient “Missing a Dose” Is Not a Step In the Dosing Regimen Claimed in the 693 Patent**

The relevant inquiry is whether the act of “missing a dose” is a step of the Asserted Claims (rather than merely a description of the object of the steps of the Asserted Claims). The law is clear that the steps of a method claim are actions that must be “carried out” for infringement to occur. *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 921 (2014). Thus, identifying the “steps” of a method claim simply means identifying what actions the patent teaches. As with any question of claim interpretation, the identification of the claim steps is a question of law and the claim terms “are generally given their ordinary and customary meaning.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted).

**1. The Structure and Grammar of the Asserted Claims Make Clear that “Missing a Dose” Is Not a Claim Step**

A method claim typically consists of: (i) a preamble that describes the conditions in which the method is practiced, and (ii) the body of the claim. *See AMAG Pharms., Inc. v. Sandoz, Inc.*, No. 16-cv-1508, 2017 WL 3076974 (D.N.J. July 19, 2017); *see also Microprocessor Enhancement Corp. v. Texas Instruments*,



*Inc.*, 520 F.3d 1367, 1374 (Fed. Cir. 2008) (“Method claim preambles often recite the [conditions] in which the claimed method is practiced.”). Structure and grammar provide clues to distinguish the method steps from the condition; generally, “the body, of a method claim [consists of] methods steps, which should usually be verbal (gerundial) phrase[s], introduced by a gerund or verbal noun (the “-ing” form of a verb).” *AMAG*, 2017 WL 3076974, at \*25.

Even putting aside the preamble, the grammar and structure of a method claim can distinguish steps from conditions. *See Core Wireless Licensing S.A.R.L. v. Apple, Inc.* No. 15-cv-5008, 2016 WL 6427850 (N.D. Cal. Oct. 31, 2016). In *Core Wireless*, the claim at issue included three separately indented clauses that began with gerunds describing actions to be taken with a core network element identifier: “storing,” “inserting,” and “sending.” *Id.* at \*3-4. The “sending” clause also included an extensive description of the type of radio network to which the core network element identifier was to be sent. *Id.* at \*4. The defendant argued that the “sending” clause contained several additional claim steps requiring configuring the receiving radio network in a certain way. *Id.* The court rejected this interpretation: “the claim’s grammar and indentation support [plaintiff’s] argument that [the receiving network parameters] describe an environment and not separate steps.” *Id.* at \*5. “The three steps identified by [plaintiff] each start on a separate line with a gerund, a verb that acts as a noun, demonstrating how the

method should be performed.” *Id.* at \*5.

The distinction between method steps and the conditions for their performance also applies to method of treatment claims. Specifically, a method of treatment claim’s description of the conditions for using the method often defines a particular population of patients to whom the drug administering steps are directed. For example, in *Orexigen*, there was no divided infringement in a method of treating obesity “comprising administering [a pair of compounds] to an individual who has been diagnosed as suffering from overweight or obesity.” 282 F. Supp. 3d at 798. Defendants argued, similar to Mylan here, that diagnosing obesity was a step of the claimed method, and that infringement was therefore divided between the doctor (who diagnoses) and the patient (who self-administers this medicine). *Id.* at 812. The court rejected this argument: “a plain reading of this claim limitation indicates that the individual will already be diagnosed prior to the method being performed. The method itself requires only the single step of administering the drug.” *Id.*

Under this case law, it is clear that a patient “missing a dose” of PP3M is not a step of the claimed method. First, the grammar and structure of claim 5 (the only independent claim asserted) establishes that the only steps in the claim are “administering” PP1M and PP3M in certain doses, at certain intervals, to certain patients:

5. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with PP3M, wherein said patient had been last administered a PP3M injection 4 to 9 months ago and the next scheduled maintenance dose of PP3M should be administered to said patient, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M;
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose; and
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose

Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M
175 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	525 mg eq.

693 Patent, col. 21. As in *AMAG*, *Core Wireless*, and *Orexigen*, the claim steps here are identified with a verbal noun (*i.e.*, a gerund): “administering.” The three instances of “administering” are separately enumerated and indented, delineating what specific steps must be *carried out* to perform the method. The claim recites no other active steps.

By contrast, there is no reference to a patient “missing a dose” at all. Rather, the condition that a patient has missed a regularly scheduled 3-month dose of PP3M is set out in the preamble: “wherein said patient [*i.e.*, in need of treatment

for schizophrenia] *had last been administered* a PP3M injection 4 to 9 months ago.” This preamble provides even stronger structural evidence than in *AMAG*, *Core Wireless*, or *Orexigen* because claim 5 here sets out the conditions for using the method separately from the enumerated claim steps. Under the plain language of the claims, the time when a patient “had last been administered” PP3M is a condition of the patient, not an action to be carried out. It is therefore not a step in the claimed methods of treatment.

**2. The Purpose of the Asserted Claims Confirms That the Plain and Ordinary Meaning Does Not Include Missing a Dose as a Claim Step**

The purpose of the Asserted Claims, as set forth in the patent itself, reinforces the plain and ordinary meaning established by the clear structure and grammar of the claim. As the preamble describes, the subject matter of claim 5 is “a dosing regimen.” It would stretch the meaning of “a dosing regimen” far beyond its ordinary and customary meaning to conclude that the fact that patient had last received PP3M 4 to 9 months ago is a step in the regimen. Taken together, the structure, grammar, and ordinary meaning of claim 5 (and the claims that depend from it) all establish that the steps of the claimed method are the three enumerated “administering” steps only. A patient “missing a dose” is not a step of the claimed method.

**3. Construing “Missing a Dose” to be a Claim Step**

### **Leads to Absurd Results**

Mylan's argument that "missing a dose" is a step in the claimed method defies common sense. Consider, for example, a method of treating cigarette addiction. Under Mylan's logic, the patient's smoking of cigarettes would be a step of that method. Likewise, a patient becoming addicted to narcotics would be a step in a claim to methods for treating addiction or overdose. And a patient's genetics, diet, and exercise would be steps in a method for treating obesity. Taking Mylan's theory to its logical extreme, a patient developing cancer would be a step in the method of treatment for cancer.

Indeed, Mylan's infringement expert, Dr. Steven Berger, acknowledged that this was Mylan's logic. Dr. Berger testified at deposition that under his analysis of methods of treatment, patient overdosing would be the first step in the method of treatment claim for treating overdose, and that such a claim would therefore be subject to a divided infringement defense:

Q. Would you consider overdosing to be the first step in a dosing regimen for a drug indicated to treat overdose?

A. Yes.

Q. And you would consider a patient to be the only person who is carrying out that step of the dosing regimen for overdose medication?

...

A. If a person intentionally overdoses, the answer is yes. If the person is in a bar and doesn't know that someone put something in his drink and he

overdoses without knowing, I can't say that the patient is the one who performs the first step.

Ex. 3 at 190:25-192:4 (Berger Tr.) (objections omitted).

Furthermore, because Mylan's divided infringement theory is untethered from the language of the claims, under Mylan's logic, such claims include potentially infinite additional steps and actors. And Dr. Berger has embraced this logic to its implausible extreme:

Q. Okay. So let's go one step at a time. You'd agree that Claim 5 states that the first step of a dosing regimen is "administering intramuscularly in the deltoid muscle of said patient a first re-initiation loading dose of PP1M," correct?

A. I agree that it says that, but that's not correct. . . . Because *the first step is to evaluate the patient*.

*Id.* at 130:17-131:5 (objections omitted).

Q. [A]t the conclusion of this process of evaluation, the prescriber will then make an overall judgment about what course of treatment to proceed with the patient, correct?

A. Or recommend, yes. . . . *There's another step* between that and this. And that is that *the patient has to cooperate and consent*.

*Id.* at 135:18-136:1.

Q. And, in this case, turning back to Claim 5, the recipe to follow is stated as a series of steps, correct?

A. Correct.

...

Q. And the second step is administering intramuscularly in the deltoid muscle a second re-initiation loading dose of PP1M on about the 4th day to about the 12-day after administering the first loading dose? Correct?

A. That's what it says, but it's incorrect. It's incomplete.

...

Q. Okay. So what's . . . incorrect about the second step, what I asked you about the second step?

A. Because all of those things that happened before the first reinitiation step have to happen again. And *there's an additional step* that has to happen and *that is that the patient has to show up*.

*Id.* at 139:23-:141:13.

All in all, Dr. Berger reads at least four additional steps for the patient into

Claim 5:

Regardless of what the label says what it says – the guidance in the label does not infringe because there's six steps that have to be covered in order to comply with Janssen's label. The prescriber is responsible for three of those steps. *And the patient is responsible for three of those steps- actually four of those steps.* The patient has to, No. 1, miss a dose, No. 2 has to come back in between month 4 and month 9 and agree to be treated once again. Step No. 3 has to come back a week later and do the same thing and No. 4 has to come back a month later and do the same thing. The patient has to miss the dose and show up for the next three doses in order to comply with Janssen's package insert.

*Id.* at 165:20-166:12.

None of these steps appears in the language of the claims and yet Dr. Berger views them as critical to infringement. Mylan's theory and interpretation of the claim render the claim language meaningless and fly in the face of the cardinal rule



of claim construction that gives primacy to the plain language of the claims. The Court should reject the construction of the claims that Mylan’s divided infringement theory implicitly invokes. *See, e.g., Cytologix Corp. v. Ventana Med. Sys.*, 424 F.3d 1168, 1172 (Fed. Cir. 2005) (“[T]he district court has considerable latitude in determining when to resolve issues of claim construction.”); *Trimed, Inc. v. Arthrex, Inc.*, No. 18-cv-666, 2021 WL 1174532, at \*6 (D. Del. Mar. 29, 2021) (collecting cases where “the Federal Circuit has repeatedly upheld a district court’s decision to revisit claim construction as the case progresses”).

**B. All of the Steps of the Claimed Method are Performed By a Single Actor**

As explained above, the Asserted Claims include only three steps. All three steps consist of administering a long-acting injectable form of paliperidone palmitate. It is undisputed that both claim 5 and Mylan’s ANDA product label instruct the same actor—a patient’s healthcare provider—to perform all three injections. Thus, Mylan’s ANDA product label instructs the performance of all steps of the claimed method by a single actor and there is no divided infringement issue in this case. Since there is no divided infringement issue presented by the 693 patent, Mylan’s divided infringement defense is irrelevant and should be precluded under Federal Rules of Evidence 402 and 403.

**III. MYLAN FAILED TO TIMELY DISCLOSE ITS DIVIDED**

## **INFRINGEMENT ARGUMENT**

The Court need not reach the merits of Mylan's theory to decide the instant motion. Mylan's divided infringement defense is untimely. Mylan simply did not disclose any theory of non-infringement based on divided infringement in its contentions as required by the Local Rules. (Nor did Mylan raise the underlying claim interpretation issue during the scheduled time for claim construction.) The law in this district is clear: Mylan was bound by the local rules to disclose its non-infringement theories in its contentions or move to amend its contentions to add new theories. Mylan did neither. Its divided infringement theory should therefore be struck.

### **A. Mylan's Divided Infringement Theory Was Not Disclosed in Its Non-Infringement Contentions or During Claim Construction**

As required by Local Patent Rule 3.6, Mylan served its non-infringement contentions on May 26, 2021. They were just five pages long, and presented two theories of non-infringement: that Mylan does not *directly* infringe the Asserted Claims because Mylan itself does not administer the claimed dosing regimen to the patient; and that Mylan does not *indirectly* infringe the claims because it does not have any control over whether patients are treated with the dosing regimen. Ex. 1 at 4-6.

As alleged support for this new theory, Mylan hangs its hat on its contention that it does not “induce any particular party to perform any particular claim step that Mylan itself does not practice, *i.e.*, administering a claimed composition.” That does not raise its theory of divided infringement. Until Dr. Berger’s rebuttal expert report, Mylan never contended that (1) missing a dose was a step of the claimed dosing regimen, or (2) that two actors (patient and doctor) are therefore required to perform the steps of the claimed dosing regimen. Mylan’s contentions include no discussion of missing a dose or of the patient’s role in the dosing regimen, whatsoever.

In fact, Mylan does not dispute that it failed to disclose the divided infringement theory in its contentions. Mylan claims instead that Janssen should have been on notice because Mylan “made clear that it was contesting indirect infringement at least in part because [it] would not induce another’s direct infringement.” Ex. 2 at 7. But Mylan’s statement that it would not “induce any particular party to perform any particular claim step that Mylan itself does not practice, *i.e.*, administering a claimed composition” does not disclose Mylan’s present contentions that the “act of missing a dose” is a claim step, that

infringement is “divided” between a patient and a doctor, or that, as a result, there is no direct infringement of the Asserted Claims.<sup>1</sup>

**B. The Court Should Strike Mylan’s Divided Infringement Defense**

Courts in this district routinely preclude testimony or strike theories that were not disclosed in contentions. *See, e.g., Chiesi United States v. Aurobindo Pharma United States*, No. 19-cv-18756, 2022 WL 304574, at \*4-5 (D.N.J. Jan. 9, 2022) (granting motion *in limine* precluding testimony on indefiniteness theory that was not disclosed in contentions); *Merck Sharp & Dohme Corp. v. Sandoz, Inc.*, No. 12-cv-3289, 2014 WL 997532, at \*9 (D.N.J. Jan. 6, 2014) (striking portions of expert reports that rely on prior art not disclosed in contentions); *Celgene Corp. v. Hetero Labs*, No. 17-cv-3387, 2021 WL 3701700, at \*17 (D.N.J. June 15, 2021) (striking invalidity theory “not set out in Defendants’ invalidity contentions” because it is “impermissible” to introduce new theories in an expert report without amendment).

The local patent rules and their disclosure requirements “exist to further the goal of full and timely discovery and provide all parties with adequate notice and

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<sup>1</sup> If Mylan had advanced this theory in its contentions, as it was required to do, Janssen could have addressed Mylan’s erroneous claim construction on which the theory is premised at the scheduled time. But neither party proposed any terms for the Court to construe during claim construction or any time thereafter.

information with which to litigate their case” as well as to “require parties to crystallize their theories of the case early in the litigation and to adhere to those theories once they have been disclosed.” *Celgene Corp.* 2021 WL 3701700, at \*19 (internal citations omitted). As this Court has previously explained, “[g]iven the purpose behind the patent local rules’ disclosure requirements, a party ***may not use an expert report*** to introduce new infringement theories . . . not disclosed in the parties’ infringement contentions. . . .” *Id.* at \*12 (internal citations omitted) (emphasis added).

The *Chiesi* case is directly on point. There, the plaintiff moved to preclude testimony on the defendant’s indefiniteness theory because it was not disclosed in contentions and appeared for the first time in a rebuttal expert report. 2022 WL 304574, at \*4-5. The defendant argued that the theory was encompassed in one of its contentions, and that regardless, the plaintiff was put on notice by the rebuttal expert report and “implicitly . . . by virtue of the questions they posed” during depositions. *Id.* at \*4.

The Court granted plaintiff’s motion *in limine* and precluded defendant from arguing indefiniteness at trial. It held that “[i]t is beyond question” that the defendant was “duty bound by the Local Patent Rules to disclose” its theories in contentions and had not done so. *Id.* at \*14-15. The Court added that “the ‘notice’

[the defendant] purport[ed] to have effected . . . is irrelevant to its compliance with the Rules.” *Id.* at \*16.

The same is true here. Mylan failed to disclose its divided infringement theory in its contentions, and has instead tried to argue that Janssen was on notice despite that failure, citing portions of Janssen’s contentions and expert reports. Ex. 2 at 7-8. In fact, Janssen’s submissions do not remotely reflect notice of Mylan’s divided infringement theory, which would have been impossible because Mylan disclosed no such theory until its rebuttal expert report. But in any event, ***Janssen’s*** submissions are irrelevant to ***Mylan’s*** failure to comply with the local rules. Mylan was “required to amend [its] contentions to the extent an expert report set out a new theory . . . not previously set out in [its] . . . contentions.” *Celgene*, 2021 WL 3701700, at \*2. Amendments under Local Patent Rule 3.7 are “made *only* by order of the Court upon a timely application for good cause.” L. Pat. R. 3.7 (emphasis in original). Mylan improperly seeks to shift Mylan’s burden of seeking leave to amend its contentions to Janssen by forcing Janssen to make this motion.

For the aforementioned reason, Janssen respectfully requests that the Court preclude any testimony on Mylan’s untimely and irrelevant divided infringement theory.



Dated: August 19, 2022

*/s/ Keith J. Miller*

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IN THE UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV, and  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

Plaintiffs,

-v-

MYLAN LABORATORIES LIMITED,  
Defendant.

:  
: Civil Action No. 3:20-cv-13103  
: GC-LHG (consolidated)  
:

FINAL PRETRIAL ORDER

CONFIDENTIAL

[Filed Under Seal]

This matter having come before the Court for a pretrial conference pursuant to Fed. R.

Civ. P. 16; and

Keith J. Miller  
**ROBINSON MILLER LLC**  
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110 Edison Place, Suite 302  
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1133 Avenue of the Americas  
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having appeared for plaintiffs, and

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having appeared for defendant; the following Final Pretrial Order is hereby entered:

**I. JURISDICTION** (set forth specifically).

This is a consolidated action brought pursuant to the patent laws of the United States, Title 35, United States Code and the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act, *see* 21 U.S.C. § 355(j). This Court has original jurisdiction over the subject

3. The infringement and validity of the Asserted Claims of the 693 Patent is governed by Title 35 of the United States Code as amended by the America Invents Act (“AIA”).
4. The 693 Patent is listed in the U.S. Food and Drug Administration’s (“FDA”) publication “Approved Drug Products with Therapeutic Equivalence Evaluations” (the “Orange Book”) in connection with Janssen’s Invega Trinza<sup>®</sup> (3-month paliperidone palmitate extended-release injectable suspension) product.
5. By letters dated August 14, 2020, July 2, 2021, and September 8, 2021, Mylan informed Janssen that it had submitted to the FDA Abbreviated New Drug Application (“ANDA”) Nos. 212290, 215682, 216228, respectively, pursuant to 21 U.S.C. § 355(j), seeking FDA approval to engage in the commercial manufacture, use, sale, offer for sale in, and/or importation into the United States of generic 3-month paliperidone palmitate extended-release injectable suspension products (“Mylan’s Proposed ANDA Products”) prior to the expiration of the 693 Patent.

#### **B. Parties**

6. Plaintiff JPI is a corporation organized and existing under the laws of the Commonwealth of Pennsylvania, having its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.
7. Plaintiff JPN is a corporation organized and existing under the laws of Belgium, having its principal place of business at Turnhoutseweg, 30, B-2340 Beerse, Belgium.
8. Plaintiff JRD is a limited liability company organized and existing under the laws of New Jersey, having its principal place of business at 920 Route 202 South, Raritan, New Jersey 08869.
9. Defendant Mylan is a corporation operating and existing under the laws of India with a principal place of business at Plot No. 564/A/22, Road No. 92, Jubilee Hills 500034, Hyderabad, India.

#### **C. The Patent-In-Suit**

10. The 693 Patent titled “Dosing Regimen for Missed Doses For Long-Acting Injectable Paliperidone Esters” issued on December 4, 2018.
11. JPN is the owner of the entire right, title, and interest in and to the 693 Patent, as issued.
12. The 693 Patent names Srihari Gopal, Paulien Gerarda Maria Ravenstijn, Alberto Russu, and Mahesh Narain Samtani as joint inventors.
13. The 693 Patent issued from U.S. Application No. 15/090,889, filed on April 5, 2016. The 693 Patent claims the benefit of Provisional Application No. 62/162,596, filed on May 15, 2015 (the “’596 Provisional”), and Provisional Application No. 62/144,054, filed on April 7, 2015 (the “’054 Provisional”).

Mylan objects to Dr. Little's testimony to the extent he attempts to opine on matters outside the scope of his Rule 26 expert report, anything outside his experience or purported area of expertise and to testimony objectionable under one or more of Fed. R. Evid. 702, 703, 401, 402 and 403. Mylan further objects to the extent Dr. Little attempts to opine or testify on legal issues that are beyond his experience and knowledge.

**3. Jogarao V.S. Gobburu, Ph.D**

Mylan objects to Dr. Gobburu's testimony to the extent he attempts to opine on matters outside the scope of his Rule 26 expert report, anything outside his experience or purported area of expertise and to testimony objectionable under one or more of Fed. R. Evid. 702, 703, 401, 402 and 403. Mylan further objects to the extent Dr. Gobburu attempts to opine or testify on legal issues that are beyond his experience and knowledge.

**4. Christian G. Kohler, M.D.**

Mylan objects to Dr. Kohler's testimony to the extent he attempts to opine on matters outside the scope of his Rule 26 expert report, anything outside his experience or purported area of expertise and to testimony objectionable under one or more of Fed. R. Evid. 702, 703, 401, 402 and 403. Mylan further objects to the extent Dr. Kohler attempts to opine or testify on legal issues that are beyond his experience and knowledge.

Mylan objects to the testimony of Dr. Kohler to the extent he intends to rely on undisclosed materials that were relevant to his analysis in this case, including individuals he spoke with about prescription habits with respect to Invega Trinza®.

**5. Carla S. Mulhern**

Mylan objects to Ms. Mulhern's testimony based on her methodology and analysis. Mylan further objects to Ms. Mulhern's testimony to the extent she attempts to opine on matters outside the scope of her Rule 26 expert report, anything outside her experience or purported area of expertise and to testimony objectionable under one or more of Fed. R. Evid. 702, 703, 401, 402, and 403. Mylan further objects to the extent Ms. Mulhern attempts to opine or testify on legal issues that are beyond her experience and knowledge.

**C. Mylan's experts are:**

**1. Steven Berger, M.D.**

[REDACTED]  
Reno, Nevada 89509

Dr. Berger is an expert in the field of psychiatry and treatment of patients with psychotic disorders, including patients with schizophrenia, psychosis, and/or schizoaffective disorder, and in the management of care of such patients with antipsychotics. Dr. Berger had at least the qualifications of a person of ordinary skill in the art at the time of the invention. His testimony will be commensurate with the scope of his expert reports, his deposition, and as necessary to

respond to the testimony and evidence offered by Plaintiffs' experts regarding infringement and secondary considerations of non-obviousness.

Dr. Berger obtained his M.D. degree from the University of Michigan Medical School in 1972 and completed his residency in 1975 at the Psychosomatic and Psychiatric Institute, Michael Reese Hospital in Chicago, Illinois. Dr. Berger has been a practicing psychiatrist continuously for 49 years. His clinical experience includes evaluating and treating patients in numerous settings including private office practice, state hospital outpatient clinics, state hospital inpatient, community mental health centers, corrections (jails and prisons), private forensic psychiatry practice, and state hospital forensic practice.

Dr. Berger currently practices medicine full-time at Lakes Crossing Center Forensic Hospital and Northern Nevada Adult Mental Health Services (NNAMHS). His work for NNAMHS includes working at various locations such as Dini Townsend Psychiatric Hospital, Mental Health Court Clinic, and the Adult Outpatient Clinic. For the last 46 years, Dr. Berger has also maintained a private practice in forensic psychiatry. The majority of his time, roughly eighty (80) percent, is spent treating patients. Dr. Berger has extensive experience treating patients with schizophrenia that spans more than four (4) decades. He has experience treating patients with long-acting injectable (LAI) antipsychotics since the 1970s and has used in his clinical practice LAIs such as fluphenazine, risperidone, aripiprazole, and paliperidone palmitate (including Invega Sustenna® and Invega Trinza®). Throughout his career as a treating psychiatrist, Dr. Berger has become an expert in the standard of care for treatment of patients with schizophrenia and the reentry of patients following lapses in prescription regimens.

Dr. Berger is certified by (i) the American Board of Psychiatry and Neurology in Psychiatry and in Forensic Psychiatry; (ii) the National Board of Physicians and Surgeons in Psychiatry and Forensic Psychiatry; (iii) the American Board of Forensic Psychiatry, C/P American Academy of Psychiatry and the Law; and (iv) the Nevada Division of Public and Behavioral Health as a Certified Evaluator of Competency to Stand Trial. In addition to his clinical experience, Dr. Berger has held several academic appointments throughout his career, including a currently maintained position as a Volunteer Clinical Professor in the Department of Psychiatry and Behavioral Sciences at the University of Nevada, Reno School of Medicine. He has also authored a book and book chapter regarding establishment of a forensic psychiatric practice in addition to publication of several articles.

Dr. Berger is expected to testify regarding the opinions and underlying facts set forth in his expert reports in this case, including, *inter alia*, his background and experience, Mylan's non-infringement position, the lack of any secondary considerations, including *inter alia*, unexpected results, long-felt but unmet need, and/or industry praise, and in rebuttal to any opinions and/or evidence offered or expressed by Plaintiffs' witnesses.

## **2. Laird Forrest, Ph.D.**

Department of Pharmaceutical Chemistry, School of Pharmacy  
University of Kansas, Lawrence, KS 66047

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

CIVIL ACTION NUMBER:

Plaintiffs,

2:20-cv-13013-EP-LHG

vs.

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

ORAL ARGUMENT

Defendants.

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
October 20, 2022  
Commencing at 1:00 p.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
UNITED STATES DISTRICT JUDGE**

1 it's carried out, but it's carried out by two different  
2 entities that are not under the same control but are acting  
3 independently, then there's no infringement. There's no direct  
4 infringement and if there's no direct infringement, there's no  
5 induced infringement. So that's the legal framework Mylan is  
6 relying on.

7           So what they're arguing now -- and part of our motion  
8 is that they weren't arguing it at the beginning of the case --  
9 but they're now arguing that there's no infringement of the  
10 Asserted Claims of the '693 patent because the steps of the  
11 claimed dosing regimen are performed by two entities acting  
12 independently. They say the patient misses a dose, that's one  
13 step, and a health care provider administers the injections --  
14 the claimed dosing regimen -- those are other steps. And  
15 according to Mylan, because the patient and the healthcare  
16 provider are allegedly acting independently, there's no  
17 infringement.

18           So the key concept behind their defense here is --  
19 the premise is that the patient missing a dose is a step of the  
20 claim method. That's the dispute between the parties and I'll  
21 get into it a little bit later in the presentation, but it's  
22 really important to emphasize that the dispute is not whether  
23 having missed a dose is a requirement or limitation of the  
24 claim. It's a patent law distinction that's very important.  
25 There's no dispute that having missed a dose is a requirement

1 to determine the admissibility of evidence without the benefit  
2 of the context of trial. The rationale underlying pretrial  
3 motions in limine does not apply in a bench trial, where it is  
4 presumed that a judge will disregard inadmissible evidence and  
5 rely only on competent evidence.

6 Without a jury, the need of an advanced ruling to  
7 exclude testimony is superfluous and unnecessary because the  
8 judge is presumably competent to disregard what he or she  
9 thinks should not have been heard or to discount it for  
10 practical and sensible reasons. Without a jury, there's little  
11 risk of prejudice or confusion, particularly because the Court  
12 may later disregard testimony in whole or in part where  
13 necessary. In fact, Courts are advised to deny motions in  
14 limine in non-jury cases. I cite 9 Charles A. Wright & Arthur  
15 R. Miller, Federal Practice and Procedures Civil, 3d § 2411  
16 (2008). The more prudent course in a bench trial is to resolve  
17 all evidentiary doubts in favor of admissibility.

18 I will deny both motions in limine, docketed entries  
19 80 and 81. Neither experts will be excluded and the parties  
20 may introduce evidence and arguments regarding a single entity  
21 infringement theory as in Janssen's case or divided  
22 infringement defense in Mylan's case. Those denials are with  
23 prejudice with one exception: Janssen has argued that Mylan's  
24 divided infringement defense should be barred because it was  
25 untimely declared under the local rules. The parties may renew

1 their arguments as to that particular issue only in their  
2 post-trial briefs.

3 Okay? Other issues that we need to resolve? I want  
4 to make sure everybody agreed to the stipulation that we had  
5 submitted and signed earlier so that I can sign it and file it  
6 under seal. That's not a problem, right? Okay. We'll do  
7 that.

8 I would like to confirm the scheduling that everybody  
9 provided on October 14, 2022 via email so we could confirm the  
10 scheduling order and that will also be under seal.

11 So the way that I have it, November 16th, we have  
12 opening presentations on infringement. That's 30 minutes for  
13 each side. Correct?

14 MR. MUKERJEE: That's correct, Your Honor.

15 MR. MILLER: That's correct.

16 THE COURT: November 16, Dr. Sommi, the plaintiff's  
17 witness on infringement, will be testifying for approximately  
18 three hours.

19 Correct?

20 MS. MULLINS: That's correct, Your Honor.

21 THE COURT: On November 30th, Dr. Berger, the  
22 defendant's witness on non-infringement will be testifying for  
23 approximately three hours.

24 Right? November 30th, your witness?

25 MR. MUKERJEE: Correct, Your Honor.



Case 2:20-cv-13103-EP-LDW Document 121 Filed 10/21/22 Page 1 of 1 PageID: 4946

**NOT FOR PUBLICATION**

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

**JANSSEN PHARMACEUTICALS, INC.,  
et al.,**

**Plaintiffs,**

**v.**

**MYLAN LABORATORIES LIMITED,**

**Defendant.**

**Civil Action No. 20cv13103 (EP) (LHG)**

**ORDER**

The parties having each moved *in limine* to, and the Court having heard oral argument, and for the reasons and to the extent set forth on the record on October 20, 2022,

IT IS, on this 20<sup>th</sup> day of October, 2022,

ORDERED that the pending motions in limine (D.E.s 80, 81) are DENIED.



Evelyn Padin, U.S.D.J.

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS,  
INC., JANSSEN PHARMACEUTICA  
NV, and JANSSEN RESEARCH &  
DEVELOPMENT, LLC,

Plaintiffs,

v.

MYLAN LABORATORIES LIMITED,

Defendant.

Civil Action No. 2:20-cv-13103-EP-  
LDW

(Consolidated)

**HIGHLY CONFIDENTIAL –  
FILED UNDER SEAL**  
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**MYLAN’S OPENING POST-TRIAL BRIEF**

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any of his residents have ever been able to follow the information provided in the Trinza<sup>®</sup> label with respect to a patient who has missed a dose and returns for treatment four to nine months after his/her last PP3M injection. *See* FOF ¶ 282. And nothing at trial—let alone on cross-examination—undermined Dr. Berger’s testimony in this regard.

Against Dr. Berger’s uncontroverted testimony, it is telling that Janssen chose to forego any testimony from a prescribing physician who had or would follow the claimed missed-dose regimen. Instead, Janssen sought testimony from a healthcare professional who does not have prescribing rights for the drug at issue: Dr. Sommi, a pharmacist.<sup>11</sup> For his part, Dr. Sommi testified that his clinical work, outside of clinical trials,<sup>12</sup> involves “giv[ing] some verbal recommendations to the nurse practitioner and the psychiatrist about what could be done in terms of managing, what [he] thinks is going on with that patient from a medication point of view, and then [he] prepare[s] a written report . . . that goes into the patient’s record.” FOF ¶ 282 (quoting Tr. 49:22-50:2 (Sommi)).

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<sup>11</sup> While Dr. Kohler testified for Janssen on secondary considerations, Janssen did not ask Dr. Kohler to testify on infringement and objected to any Mylan questioning on that topic. FOF ¶ 62; *see also* FOF ¶ 64.

<sup>12</sup> And as Dr. Sommi testified, in the case of clinical trials, these are patients who are different from those in the real-world because in clinical trials they are “all patients who were actively engaged in wanting to get injections.” FOF ¶ 282; Tr. 648:11-13 (Sommi).

developing a PP3M product would use the known techniques from PP1M and apply them in the same way. *KSR*, 550 U.S. at 416. That is exactly what Dr. Forrest did. FOF ¶ 384-85.

**The four-to-nine month patient population:** It should not go unnoticed that, for the purposes of infringement, Janssen does everything it can to argue that the four-to-nine month portion of the preamble is simply a “clinical descriptor” of who the claimed methods are applied to. Yet, for invalidity, Janssen transforms that time frame into the proverbial golden goose, arguing that that no POSA would be able to determine that claim element absent thousands of clinical data points. FOF ¶ 50. That cannot be; Janssen cannot have it both ways. But, if Janssen is correct that this is not a step of the claim but remains an element that Mylan must prove is invalid, the prior art would have led a POSA to this four-to-nine month window. *See* Section III.B.5.

**Using PP1M after a patient advanced to PP3M:** Janssen’s argument here, again, overreaches in the required proofs. Mylan concedes that no prior art disclosed *exactly* what is claimed in the ’693 patent. But that is not the test for obviousness. The test is whether a POSA would have been led by the prior art to the claimed subject matter. Here, the prior art taught that the FDA approved PP1M as a dosage that could be used as loading doses for a patient that missed a previous maintenance dose and was at risk of drug concentration dipping below the previous steady state. FOF ¶ 370. Whether the previous maintenance dose was a PP3M or

PP1M is immaterial. The point of using PP1M as a loading dose is to get the patient's drug concentration back to a steady state as quickly as possible. FOF ¶ 369. And the prior art taught that that could be done with two PP1M doses, one week apart. FOF ¶¶ 349, 351, 353. Moreover, general pharmacokinetic knowledge teaches using a faster-acting injectable for loading doses. FOF ¶¶ 151, 171. As such, a POSA would expect that a PP1M formulation would be faster-acting than a PP3M formulation due to its smaller particle sizes. *Id.*

**Using PP3M without stabilizing with four or more months of PP1M:**

Janssen spent little time on this purported deficiency in the prior art. That too is not surprising. The JAMA prior art taught that for, initiating a patient, one would be stabilized with four or more months of PP1M. FOF ¶ 365. But a POSA certainly would not treat a patient that has drug in his or her body already in the same way. FOF ¶ 384. Instead, a POSA would know from the PP1M Prior Art that, in such a situation, two successive reinitiation loading doses of PP1M, one week apart, would return a patient to steady state. FOF ¶¶ 349, 351, 353. So treating a patient as naïve after four or more months of PP1M administration would not make sense to, or be advanced by, a POSA. FOF ¶ 161. Further, courts do not look to prior art in the “narrow, rigid” manner Janssen seeks to forward here. *KSR*, 550 U.S. at 420. “It is common sense that familiar items may have obvious uses beyond their primary purposes” and the initiation regimen for PP3M taught by JAMA—which uses PP1M to stabilize patients for a period of four months prior to their maintenance

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV, and  
JANSSEN RESEARCH &  
DEVELOPMENT LLC,

*Plaintiffs,*

v.

MYLAN LABORATORIES LTD.,

*Defendant.*

Civil Action No. 2:20-cv-13103  
(EP)(LDW)

FILED UNDER SEAL

**PLAINTIFFS' OPENING POST-TRIAL BRIEF**

*GlaxoSmithKline*, 744 F.3d at 731 (distinguishing case “where the claim covered particle sizes before and after formulation into tablets, but the specification addressed only pre-formulation size”).

Finally, to the extent that Mylan contends there are insufficient examples to demonstrate written description, Mylan is incorrect.

There is no requirement that the disclosure contain either examples or an actual reduction to practice; rather the critical inquiry is whether the patentee has provided a description that in a definite way identifies the claimed invention in sufficient detail that a person of ordinary skill would understand that the inventor was in possession of it at the time of filing.

*Alcon*, 745 F.3d at 1190-91 (internal quotation marks omitted). FOF 386-87. The inventors described PP1M and PP3M in sufficient detail to demonstrate they possessed the invention at the time. FOF 288. Mylan’s cursory written description case failed to meet its burden of proving invalidity by clear and convincing evidence.

**V. MYLAN’S DIVIDED INFRINGEMENT DEFENSE SHOULD BE STRICKEN**

Mylan’s divided infringement defense is untimely and should be stricken for the reasons set forth in Janssen’s motion *in limine* (D.E. 81), which the Court denied without prejudice to raise the timeliness objection in post-trial briefing. (Oct. 20, 2022 Hr’g Tr. 55:25-56:2.) In order to pursue this undisclosed theory, Mylan was “required to amend [its] contentions,” *Celgene Corp. v. Hetero Lab ’ys Ltd.*,

No. 17-cv-3387 (ES)(MAH), 2021 WL 3701700, at \*2 (D.N.J. June 15, 2021), which would have required an Order of the Court following a showing of good cause. L. Pat. R. 3.7. Mylan sought no such amendment, so its divided infringement theory must be struck for lack of timely disclosure under the Local Patent Rules. *See Chiesi USA, Inc. v. Aurobindo Pharma USA, Inc.*, No. 19-cv-18756 (ZNQ)(LHQ), 2022 WL 304574, at \*4-5 (D.N.J. Jan. 9, 2022); *accord Merck Sharp & Dohme Corp. v. Sandoz, Inc.*, No. 12-cv-3289 (PHS)(LHG), 2014 WL 997532, at \*9 (D.N.J. Jan. 6, 2014).

The prejudice and waste caused by Mylan’s failure to follow the Local Patent Rules was evident at trial, where Mylan unveiled a “seven step” interpretation of the Asserted Claims that had never been disclosed during discovery. *See supra* at 12-20; FOF 63-65. Disputes over the number of steps in a method claim “fit[] squarely within the claim construction framework” and should have been addressed pretrial. *In re Biogen*, 2016 WL 7340311, at \*5. But because Mylan failed to follow the pretrial schedule, the parties and the Court are now in the position of having to litigate and resolve this issue at trial and in post-trial briefing. The entire purpose of pretrial disclosure rules is to avoid this outcome. *See, e.g., Bristol-Myers Squibb Co. v. Apotex, Inc.*, No. 10-cv-5810 (MLC)(LHG), 2013 WL 11897791, at \*2 (D.N.J. Feb. 28, 2013). Janssen respectfully requests that the Court enforce the Local Patent Rules by striking Mylan’s untimely divided infringement defense.



UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

CIVIL ACTION NUMBER:

Plaintiffs,

2:20-cv-13013-EP-LHG

vs.

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

BENCH TRIAL VOL. 1

Defendants.

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
November 16, 2022  
Commencing at 10:00 a.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
UNITED STATES DISTRICT JUDGE**

1 degree of side effects and these can be debilitating. These  
2 can be Parkinsonian-like movements, muscle contractions, facial  
3 involuntary contractions. This, itself, the side effects of  
4 the treatment, can be a strong deterrent to actually getting  
5 treatment and there is a stigma associated with those side  
6 effects.

7 For various safety and tolerability reasons, for many  
8 patients, second generation antipsychotics are a better choice.  
9 These act a little bit differently than first generation  
10 antipsychotics. They do carry a risk of side effects, but they  
11 tend to be not as severe. The second generation drugs also  
12 seem to work a little bit better in controlling the symptoms of  
13 schizophrenia.

14 So the very first second generation long-acting  
15 antipsychotic was actually Janssen's Risperdal Consta product.  
16 That was brought to market in 2003 and requires an injection  
17 every two weeks.

18 In 2009, Janssen released Invega Sustenna, and that's  
19 a paliperidone palmitate correlation of one once-a-month  
20 maintenance formulation or PP1M.

21 Then in 2015, Invega Trinza was released. That's  
22 also a paliperidone palmitate. It was the first and is still  
23 the only three-month long-acting antipsychotic on the market,  
24 or PP3M.

25 More recently, in 2021, Invega Hafyera was released,

1 and that's a six-month paliperidone product.

2 The products we're going to be talking about for the  
3 most part in this case are Invega Sustenna or PP1M and Invega  
4 Trinza or PP3M. These are both depot or long-acting  
5 paliperidone palmitate formulations. The way they work, just  
6 very generally, is that they are injected and when they're  
7 injected into the body, they form a depot or repository.  
8 Active drug is then released. And for these drugs, at  
9 different rates, at different times, but it's released into the  
10 body, and the drug is absorbed into the plasma or into the  
11 bloodstream where it is ultimately -- I have my man doing this.

12 THE COURT: I'm following you.

13 MS. MULLIN: -- where it is ultimately simultaneously  
14 circulated, distributed, metabolized and ultimately excreted.  
15 These four things, absorption, distribution, metabolism and  
16 excretion, these all affect how much drug is in the patient's  
17 bloodstream at any point in time. That's important because it  
18 tells you how much drug is available for any therapeutic effect  
19 at any given point in time.

20 The idea with these long-acting injectables is if you  
21 take your injections on time, if you show up about every month  
22 for Invega Sustenna, if you show up about every three months  
23 for Invega Trinza, then your plasma concentrations of drug are  
24 going to stay in the therapeutic range and everything is going  
25 to be fine.

(DIRECT EXAMINATION)

BY MS. MULLIN:

Q. Dr. Sommi, could you please introduce yourself to the Court?

A. Sure. My name is Roger Sommi. I am a pharmacist by training. I'm a psychiatric pharmacist by specialty. I'll start I graduated in 1983 with a bachelor's degree in pharmacy. Got interested in psychiatric pharmacy and treating psychiatric patients when I was there and decided let's go do a Doctor of Pharmacy degree, which I received at the University of Utah. And I also did a residency in hospital pharmacy at the University of Utah hospitals and then went on to the -- I continued my work with mentally ill folks and wanted to learn how to do research and take care of those patients at a higher level and went to the University of Texas at Austin where I completed a fellowship in psychiatric pharmacy. And I've been on the faculty of University of Missouri-Kansas City School of Pharmacy since then.

Q. Dr. Sommi, for our court reporter, I'm going to ask you to slow down just a little bit.

A. Okay. Usually it's not my forte of speaking fast.

Q. You referred to the University of Missouri-Kansas City. For short, can we refer to that as UMKC?

A. We all do.

Q. Thank you.

1 Are you Board Certified?

2 A. I am Board Certified in psychiatric pharmacy, yes.

3 Q. Can you briefly describe your teaching experience at UMKC?

4 A. So I teach anywhere from pre-pharmacy students through the  
5 first year pharmacy all the way through the end. Importantly,  
6 I teach in a capstone course called pharmacotherapy, and  
7 pharmacotherapy is where we teach our students how to take care  
8 of patients. It's a three-semester course. We talk about  
9 patients, patient characteristics, drug therapy for those  
10 patients. I teach the psychiatric sessions -- the psychiatric  
11 lectures.

12 I also teach in the clinical setting. We have  
13 students that come to the hospital for their clerkships. These  
14 are -- they would come to our psychiatric facility where the  
15 students would learn how to take care of patients who have  
16 psychiatric illness.

17 Q. Can you describe just in a little more detail your  
18 responsibilities for the clinical instruction?

19 A. Sure. So at the hospital, over the course of my career in  
20 the hospital, we have students from many disciplines. We've  
21 got medical students, nursing students, social work students,  
22 physical therapy, occupational therapy, pharmacy students  
23 obviously. We -- so for instance, with the medical students,  
24 we have a weekly meeting with the medical students to talk  
25 about drug therapy, going over general principles of drug

1 therapy for all of the major psychiatric illnesses with the  
2 pharmacy students. Speaking with the pharmacy students, we  
3 meet with them every day. We take them to rounds as we see  
4 patients. So then from a student perspective, we would be  
5 interacting with the students professionally.

6 At the hospital, we also have a psychiatry residency  
7 program. These are physicians who graduated medical school and  
8 they're in their four-year training program to become  
9 psychiatrists. Our group of psychiatric pharmacists provides a  
10 semester-long psychopharmacology course. I teach in that  
11 course. I teach the pharmacodynamics and pharmacokinetics and  
12 then, you know, other miscellaneous topics depending on the  
13 year, who wants to do what with the psychiatry residents.

14 We also have a psychiatry pharmacy residency program.  
15 This is where we're teaching students who are post graduate  
16 year two pharmacists. They already have their Pharm D degree,  
17 they've done a year of residency, and now they want to learn  
18 how to take care of patients who are mentally ill. So we have  
19 a residency program. We have two residents at the hospital in  
20 Kansas City for behavioral medicine.

21 I also work with Fulton State Hospital, which is a  
22 couple hours away, with their resident and teach them about all  
23 different kinds of psychiatric medicines.

24 Q. Are you still on the faculty at UMKC?

25 A. At this point, I am.

1 Q. Do you have any teaching responsibilities outside of UMKC?

2 A. Sure. So there's a few highlights. One is twice a month  
3 we have an interprofessional online teaching. It's called the  
4 ECHO program. The ECHO program basically is where we're  
5 connecting with other health care professionals. There's a  
6 team of us, psychiatrists. We have psychologists,  
7 psychiatrists, got peer support specialists, myself as the  
8 pharmacist, and we interact with people. We've got people that  
9 connect from Connecticut to our Zoom meeting, and we present  
10 cases. We do a little bit of a didactic presentation that  
11 happens twice a month. It's going to continue to be ongoing.

12 I do some training with local law enforcement.  
13 There's a program called Crisis Intervention Team, and the  
14 Crisis Intervention Team is law enforcement that's specifically  
15 trained to do a week-long training to -- the initial concept  
16 was to reduce the number of people who were killed by law  
17 enforcement.

18 So I go in, my section, I give them a primer on, you  
19 know, psychopharmacology. And we do a little bit of  
20 pharmacokinetics actually when we talk about overdoses and what  
21 you need to worry about from a pharmacokinetic point of view  
22 for an overdose and then we talk about how to manage and what  
23 do you need to be worried about when you're working with  
24 somebody who's taking medicine in the community.

25 Then I also do lots of national presentations over

1 the course of my career at various pharmacies, psychiatry,  
2 nursing, general kinds of conferences.

3 Q. Outside of UMKC and your responsibilities there, are you  
4 involved in any patient care?

5 A. Yes. So patient care has evolved over the years. I have  
6 taken care of patients as inpatients and taken care of patients  
7 as outpatients. More recently, most of the care that we  
8 provide to our patients has been in our clinical trial work.  
9 So when we have patients who are enrolled in our studies and we  
10 give them the experimental medication, they come and see me  
11 once a week or once every other week. It depends on what the  
12 protocol says we should be doing.

13 I also have a consultant practice at a place called  
14 Southwest Missouri Psychiatric Rehabilitation Center. This is  
15 a rural mental health center, 27, 28 beds. We meet once a  
16 month. Actually, I'm going to meet tomorrow. What they do is  
17 they identify patients that are struggling for whatever reason,  
18 whether it be -- and many times, the reason is we're not sure  
19 what to do with their medications, and so I run the meeting.  
20 So tomorrow, we'll probably do it by telemedicine with me and  
21 the patient there.

22 So I do the interview, I ask all the questions, and  
23 in the end, I give some verbal recommendations to the nurse  
24 practitioner and the psychiatrist about what could be done in  
25 terms of managing, what I think is going on with that patient



1 from a medication point of view, and then I prepare a written  
2 report and send that and that goes into the patient's record.

3 Q. You mentioned clinical trials.

4 What kind of clinical trials have you been involved  
5 in?

6 A. So clinical trials have been the main support of our  
7 research program. When I came to UMKC 35 years ago, as an  
8 assistant professor, the expectation is you develop a research  
9 program to support your work and so we've had a continuously  
10 funded clinical trials program for 35 years. It's now not  
11 funded because of my pending retirement, but we won't go into  
12 that.

13 But we've got -- most of my work almost exclusively  
14 has to do with drugs for the treatment of schizophrenia. I've  
15 worked with drugs that still don't have a name. I've worked  
16 with drugs that failed. I've worked with drugs that came to  
17 the market. We work with lots of different drugs as new  
18 formulations came along. We got the regular quick-acting  
19 injections. We got the melty tabs, the orally disintegrating  
20 tablets. We've worked with those. We've worked with a number  
21 of long-acting injectables. We've worked with drugs that are  
22 add-ons for cognitive improvement. We've done lots of  
23 different things.

24 Most recently, sort of towards the end of my career,  
25 I came to UMKC wanting to do work with drug treatment of

1 tardive dyskinesia. I ended my career actually doing work when  
2 drug treatment within for tardive dyskinesia because there's  
3 new drugs for that.

4 Q. You mentioned tardive dyskinesia, so now you've got to  
5 explain it, please.

6 A. Okay. So tardive dyskinesia is a -- so the word "tardive"  
7 means delayed in onset and "dyskinesia" means unusual movement.  
8 So it's movements that are delayed in onset typically months to  
9 years after a person begins taking their antipsychotic  
10 medication.

11 When I was in training, I was impressed with the  
12 range of movements. We had patients who rocked and, you know,  
13 but oral facial dyskinesias are really pretty prominent in  
14 tardive dyskinesia. You see tongue protrusion and lip smacking  
15 and excessive blinking. It can affect your diaphragm. It can  
16 affect your breathing. It can affect your ability to put your  
17 clothes on. It can affect your ability to eat.

18 So that's what I started my career doing and actually  
19 ended my career finding -- working with a drug that actually  
20 works.

21 Q. You mentioned clinical trials.

22 Just to be clear, were any of those clinical trials  
23 involving antipsychotics?

24 A. Almost all of those were.

25 Q. Were they Janssen drugs or drugs by other manufacturers?

1 A. Some of Janssen's, but a lot by other companies.

2 Q. Has any of your research ever been published?

3 A. Sure, a lot of it has been published.

4 Q. Is there any particular publication that stands out in  
5 your mind?

6 A. Well, so there's a study that I was proud to be a part of.  
7 I was the only pharmacist principal investigator in this  
8 particular study. This is a study called the CATIE study.  
9 CATIE stands for Clinical Antipsychotic Treatment Intervention  
10 Effectiveness, which it sounds complicated but actually is very  
11 simple. It was a -- we always wanted to have a study that  
12 compared drugs we have had. So luckily, we never had those  
13 studies. That was going to be the evidence. Is there any drug  
14 that is better than any other drug on the market? This was the  
15 study that was going to set out to prove it.

16 So I was one of 150 investigative sites. We enrolled  
17 patients into the study. And so it's a multicenter kind of  
18 trial, and to date, there's been at least 350 publications that  
19 have come from that data set. It's a very, very rich source of  
20 information about treating folks who have schizophrenia.

21 Yeah, so that group of publications, that particular  
22 study is sort of what I think of as the most important work  
23 that I've ever done.

24 Q. Can you estimate how many patients you've been personally  
25 involved with in treatment?

1 A. Thousands.

2 Q. Dr. Sommi, in front of you, there should be a binder where  
3 we can also bring up on the screen, but if I could direct your  
4 attention to what's been marked as Plaintiffs' Exhibit 128A.

5 Go to the next page.

6 You do have a screen in front of you. Can you see  
7 that, Dr. Sommi?

8 A. I can.

9 Q. Do you recognize that document?

10 A. It's the first page of a relatively recent curriculum  
11 vitae.

12 Q. Your curriculum vitae?

13 A. Mine, yes.

14 Q. Can I also then -- I'd like to direct your attention to  
15 two paragraphs in the final pretrial order that was filed with  
16 the Court, paragraphs 49 and 50, if we could bring those up.

17 This is in the stipulated facts, and paragraphs 49  
18 and 50 involve the definition of a person of ordinary skill in  
19 the art or POSA.

20 Do you understand that?

21 A. I do.

22 Q. Do you consider yourself to be qualified under either or  
23 both definitions of a POSA?

24 A. I do.

25 MS. MULLIN: Your Honor, at this time, we proffer Dr.

1 Roger Sommi as an expert witness in pharmacy in the treatment  
2 of patients with psychiatric disorders, including treating  
3 psychotic disorders such as schizophrenia with antipsychotics.

4 THE COURT: No objection?

5 So noted.

6 MS. MULLIN: Thank you.

7 BY MS. MULLIN:

8 Q. Dr. Sommi, let's talk about schizophrenia.

9 Can you give us just a general description? What is  
10 schizophrenia?

11 A. So schizophrenia is considered to be one of the psychotic  
12 disorders. It affects about 1% of the population. It's about  
13 equal males to females. There isn't any particular group  
14 that's left out of the spectrum of schizophrenia. The core  
15 symptoms are positive, negative symptoms, cognitive symptoms,  
16 mood symptoms, and all of those play together to effect the  
17 person's ability to be successful in employment and education  
18 and relationships and just day-to-day functioning.

19 Q. Can you give us some examples of positive symptoms?

20 A. So positive symptoms are things that are sort of added.  
21 So these are delusions, which are false beliefs, oftentimes  
22 paranoid delusions, persecutory delusions. They can be  
23 hallucinations. In schizophrenia, typically we see auditory  
24 hallucinations, but you can see all five senses. Those would  
25 be the positive symptoms.

1 Q. Can you give us some examples of what would be considered  
2 negative symptoms?

3 A. So negative symptoms are where we're taking things away,  
4 so alogia, poverty of speech; avolition, poverty of movement.  
5 So they're withdrawn, they don't talk very much, they are not  
6 engaged in relationships.

7 Q. Is there a standard reference for defining schizophrenia?

8 A. For the Diagnostic and Statistical Manual, or DSM, is  
9 where you find the diagnostic criteria.

10 Q. In terms of the symptoms, are they generally short term,  
11 long term, when someone has schizophrenia?

12 A. So schizophrenia is oftentimes referred to as a  
13 neuro-progressive or neurodegenerative disease, depending on  
14 how you're looking at it. So you'd have some prodromal  
15 syndrome -- prodromal symptoms that in some of the folks can  
16 occur. Looking back, they really start in high school and then  
17 they progress into their 20s when they have their first  
18 psychotic break.

19 Q. Before somebody has their first psychotic break, are there  
20 generally signs that the person is ultimately going to develop  
21 schizophrenia?

22 A. Again, it's mostly looking back. So if you look back, you  
23 can say oh, yeah, that was -- so you made the reference in your  
24 opening statement to in high school, it's 1%. If you had  
25 graduated with a class of 300, that's three students. Looking

1 back now, you could probably put your finger on the people who  
2 went on to develop schizophrenia. These are the kids who were  
3 withdrawn; they were a little bit different from everybody  
4 else. They didn't perform well in school academically.

5 Q. Can families of the patient be blindsided by the  
6 diagnosis?

7 A. Sure. I have a friend and he is my age, in high school,  
8 his brother -- so this is the family that had the golden touch,  
9 right? Father did very well in the insurance business. When  
10 my friend went to medical school, his brother gets accepted to  
11 MIT.

12 I lose track of the family and come back and meet  
13 with them again, you know, ten years later. I find that the  
14 brother, the younger brother that was going to MIT now lives  
15 with dad because he has schizophrenia. He had a psychotic  
16 break during his first semester at MIT.

17 Q. So what's it like for the family and friends of a patient  
18 or a person with schizophrenia?

19 A. It's devastating. They lose the person that they had  
20 hoped for.

21 Q. Is there a cure?

22 A. There's no cure.

23 Q. So what do health care professionals try to do?

24 A. Well, so if you're in my pharmacotherapy class and I'm  
25 giving you the lecture on schizophrenia and I talk about what's

1 independent apartment, they may be employed. But those are  
2 typically people who are engaged in treatment and stay on the  
3 medicine.

4 Q. Is there any burden on society?

5 A. Sure. You know, you have the -- these folks who are way  
6 less employed. They have a dependence on Medicaid and  
7 Medicare, typically, to pay for their treatments. They're on  
8 disability to a greater extent than the general population.  
9 Right? So we talked about 1% of the population with  
10 schizophrenia and they make way -- a way bigger percent of the  
11 patients on disability. Right? So there isn't this one-to-one  
12 relationship, so 1% of people on disability have schizophrenia.  
13 It's more percentages than that.

14 Q. So I want to then go back and talk about treatment. Okay?

15 A. Sure.

16 Q. Can you briefly describe the antipsychotics that are  
17 available or have been available?

18 A. All right. So the first antipsychotic to the market that  
19 everybody knows is Thorazine. All right. Chlorpromazine came  
20 in the '50s, sparked the creation of this group of  
21 antipsychotics that we call the first generation of  
22 antipsychotics. And so what we learned about schizophrenia and  
23 the treatment of schizophrenia from Thorazine is that if you  
24 look at the pharmacology of Thorazine, it decreases or blocks  
25 dopamine and dopamine receptors. And so there was this push to



1 find other drugs that blocked dopamine receptors and there was  
2 a bunch of them, right, and the last one being Haldol that came  
3 and -- well, Haldol wasn't actually the last one. Melinda was  
4 the last one, but that's besides the point.

5 All right. So we've got this group of drugs; their  
6 primary target is dopamine. So the challenges with the  
7 first-generation drugs is they weren't all that different from  
8 each other pharmacologically. And secondly, they had a high  
9 incidence of what we call extrapyramidal side effects or EPS.  
10 And so these are acute dystonic reactions, which are spasms  
11 that occur early on in treatment.

12 We have pseudoparkinsonism, which is so named because  
13 the pathophysiology and the symptoms look very much the same.  
14 These are the tremors that people have, they feel stiff, slowed  
15 down, they look depressed even though they aren't depressed.

16 Akathisia, which is this feeling of inner  
17 restlessness that when you cause that, can lead to suicide in  
18 the worst case because they just feel like they can't get away  
19 from themselves. And then, finally, the tardive dyskinesia,  
20 which I talked about before.

21 So there was a goal then to find a set of drugs or a  
22 different pharmacologic mechanism to sort of mitigate against  
23 that. Right? So the second generation antipsychotics all came  
24 to the market, at least the early ones came to the market with  
25 this idea that if we had some kind of serotonin activity, that

1 that, in and of itself, will mitigate against this  
2 extrapyramidal kind of side effects. And, in fact, that's what  
3 we observed. Right? Way less of all those things. So we went  
4 on happily and started treating these folks.

5 The reward we got for that is, at least the early  
6 drugs in the second generation class had problems with  
7 metabolic side effects, weight gain, changes in lipids, risk  
8 for diabetes, increases in blood glucose. And so we sort of  
9 traded tardive dyskinesia for this metabolic problem.

10 And then the more recent ones have sort of tried to  
11 get away from that. Right? And so now we have drugs that are  
12 pretty metabolically neutral and don't have any extrapyramidal  
13 effects. What we didn't get in that is a drug that's more  
14 effective. The patients tolerate it better, and so they take  
15 it, but it's not curing any more people.

16 Q. Okay. Just focusing then on long-acting injectable  
17 antipsychotics, how long have they been around?

18 A. Since the '60s.

19 Q. And what were the --

20 A. Like me.

21 Q. -- first -- what were the first long-acting injectable  
22 antipsychotics?

23 A. So the two long-acting inject -- first generation  
24 antipsychotics are Haldol decanoate and Prolixin decanoate and  
25 they're still on the market and they continue to currently be

1 used.

2 Q. Are they first or second generation?

3 A. Those are first generation drugs. Not to get down too  
4 much into the details, but these are drugs that are designed  
5 with a sesame oil base. Right? So the molecules, Haldol  
6 decanoate and Prolixin decanoate are dissolved in sesame oil  
7 and then injected into the patient. The challenge with that is  
8 that you have to inject using a specific method so the oil  
9 doesn't leak back out of the hole. That's more painful.

10 And then when you -- after you've injected and all  
11 the drug's been released from that site, that sesame oil stays  
12 there and creates a nodule in the patient, you know, underneath  
13 the skin in the muscle of that patient.

14 So those are -- and we knew that there were long --  
15 lots of complaints about it, and so there was an opportunity  
16 there in the market to create something that didn't have all  
17 those problems.

18 Q. When did second generation long-acting injectables come to  
19 the scene?

20 A. If I could look at your slide again, I would know the date  
21 that Risperdal Consta came out. 2006? Is that right? 2004?

22 Q. Would you agree with me, 2009?

23 A. 2009?

24 Q. Yes.

25 A. Yeah. So Risperdal Consta was the first second generation

1 drug to come to the market and the advances there were that it  
2 was an aqueous or water-based suspension. All right?

3 So a suspension is where you've got little particles,  
4 kind of like a snow globe. Right? You suspend it up and those  
5 particles stay floating long enough for you to inject it into  
6 the patient and then the water just dissipates because it's  
7 just water. So the water goes away, but then those little  
8 particles stay at the site of injection and then slowly  
9 dissolve. That's the process.

10 THE COURT: No nodule?

11 THE WITNESS: No nodules, right. And less painful  
12 because you don't have that extra little strategy for the  
13 injection.

14 BY MS. MULLIN:

15 Q. Dr. Sommi, is it possible that Risperdal Consta came on  
16 the market in 2003, since I've been corrected?

17 A. I said '04. I'm just pointing out I was closer than you  
18 were.

19 Q. So are all oral antipsychotics also available in  
20 long-acting injectable form?

21 A. No.

22 Q. How many of them are or are not?

23 A. Well, so if we look at molecules, right, so we've got the  
24 Haldol and the Prolixin. We've got Risperdal Consta, which is  
25 risperidone. Risperidone, when it's in the body, the

1 metabolite, right, when it gets metabolized, it creates  
2 paliperidone. So risperidone and paliperidone are not quite  
3 interchangeable, but they're related. Right? So we have our  
4 risperidone, paliperidone series. I like to lump them into  
5 that series. And then you have the aripiprazole. Right? You  
6 have the Abilify Maintena, you have Aristada. And then you  
7 have olanzapine or Zyprexa pamoate.

8           So then you also have another risperidone injection  
9 called Perseris that's on the market.

10 Q.   So in terms of how many orals compared to how many  
11 injectables, do you have any idea what that ratio is?

12 A.   No, but it's pretty low. You have aripiprazole,  
13 olanzapine, risperidone, and paliperidone. You've got four  
14 molecules versus about 13, 14.

15 Q.   Thirteen or 14 being the oral medicines?

16 A.   Just the second generation orals, yeah.

17 Q.   Okay. So in terms of your experience, over 40 years, has  
18 there been any change in attitude or acceptance for long-acting  
19 injectables?

20 A.   Well, when I -- as I tell a story about my mom, who was a  
21 nurse, and she -- I never liked the oral formulation of  
22 amoxicillin, you know, the bubble gum suspension. Not my deal.  
23 I still to this day don't like bubble gum. But I was also the  
24 kid that got strep throat a lot. And my mom would say to me:  
25 You either take the bubble gum or we're going to take you back

1 Interaction Effectiveness Study. Effectiveness is sort of this  
2 notion that effectiveness of a drug is its real-world use.

3 So in the CATIE study, we had one outcome. You were  
4 either taking your medicine or you stopped taking your  
5 medicine. Right? And no surprise, I mean, everybody was put  
6 on oral; long-acting injectables was not a part of this. Over  
7 the course of 18 months, 75% of patients had stopped taking  
8 their medicine. No surprise, right? And there wasn't any drug  
9 that was any better, right?

10 And so the effectiveness really tells us about, you  
11 know, real-world things. Relapse prevention, either you  
12 relapse or you haven't relapsed. That's an effectiveness  
13 measurement. Right? And that's in contrast to efficacy.  
14 Efficacy is the ability of a drug to reduce symptoms as rated  
15 on a rating scale.

16 Q. Can you explain the rating scales that are used?

17 A. Well, so, for antipsychotics drugs, the primary rating  
18 scales that we use are the Positive and Negative Syndrome Scale  
19 or the PANNS.

20 Q. Would that be PANSS in all caps?

21 A. That would be the one.

22 And then BPRS, which is the Brief Psychiatric Rating  
23 Scale, BPRS. So both of these have structured clinical  
24 interviews. They talk about, you know, anywhere -- when I do  
25 them, they're anywhere from an hour-and-a-half- to three-hour

1 interviews. Depends on the patient and how talkative they are.  
2 But then we rate on a Likert scale, right, on a scale of one to  
3 seven, how delusional is this person, how educated is this  
4 person, how excited is this person, how much anxiety do they  
5 have, and you come up with a score and then you do that at  
6 baseline and a drug study and it gives you a score and it tells  
7 you a little bit about the severity of their illness. And then  
8 you watch that score go down over the course of time and that's  
9 how we rate efficacy.

10 Q. How long have those scales, the PANSS, the BPRS scales,  
11 been used?

12 A. Longer than I've been around, so quite a while.

13 Q. Just very briefly, are there advantages to using  
14 long-acting injectables?

15 A. Sure. So from the overall perspective, when you look at  
16 real-world studies, long-acting injections, patients on  
17 long-acting injections have less relapse. They have less  
18 relapse. If you believe in the neurodegenerative,  
19 neuroprogressive concept of schizophrenia, the more relapses  
20 you have, more progression you have.

21 So, in theory, we should be able to show over the  
22 course of time with long-acting injections, that we're losing  
23 less and less and less brain.

24 There's a psychiatrist that I have worked with over  
25 the years that said every time a patient has a -- a patient

1 with schizophrenia has a relapse, it's like scooping out a  
2 teaspoon of brain and tossing it out because when the brain has  
3 psychosis, it's overexcited and you have cell death.

4 And so if we can prevent some of that, then certainly  
5 the prognosis would be better. Another advantage from a  
6 patient perspective is convenience. I only have to take a shot  
7 once a month, I only have to take a shot, you know, however  
8 often that particular drug is. Right? Once a month, once  
9 every three months, once every two months, whatever it is. So  
10 convenience for the patient.

11 From a caregiver point of view, the advantage of  
12 long-acting injections is less discussions about medication.  
13 Right? Because oftentimes, a caregiver is the person who's  
14 responsible for giving the oral medicine and there's a  
15 conversation that happens: It's time for your medicine; I  
16 don't want to take my medicine. Okay, well, look, we've been  
17 through this before. Well, today, I want to take my medicine;  
18 tomorrow, I don't. You know, so there's this conversation.  
19 That's -- the medicine's twice a day, that's 60 conversations a  
20 month, right, that you've got to have with that patient.

21 With the long-acting injections, that's once a month,  
22 once every two months, three months, six months, whatever, you  
23 know, the product they happen to be taking. So less care giver  
24 burden.

25 From a clinician point of view, I know that the



1 patients are getting their medicine because the medicine has to  
2 be given by a health care professional. Right? So somebody  
3 has to give that patient. If they don't show up, then I can be  
4 alerted or the physician can be alerted that, yes, in fact,  
5 this patient is late for their dosing; go out and find them.

6 I also -- I make better decisions with long-acting  
7 injections because I know that they're actually taking the  
8 medicine. Right? So I'll give you this scenario that I'm  
9 often faced with, and then when I ask the question, people are  
10 like, I don't know. Right?

11 So this is the scenario: The patient's taking the  
12 medicine -- or prescribed the medicine. They don't respond or  
13 they have a partial response, so they get a little bit better  
14 but not enough better, and so then they tried something else.  
15 So they up the dose and they started adding medicines.

16 And then I asked the question: Has anybody checked  
17 the pharmacy fill rates? No. So I go check the pharmacy and,  
18 in fact, the patient hasn't shown up to pick up any of these  
19 medicines that we have increased the dose, changed the  
20 medicine, augmented therapy, and I'm like, well, we didn't do  
21 anything because the patient didn't take any medicine. Right?

22 So we make better clinical decisions about how the  
23 patient is responding to the medicine when they're given it by  
24 injection. It's just easier for us as clinicians to make those  
25 decisions.

1 Q. Very briefly, what is Invega Sustenna? Very briefly.

2 A. Invega Sustenna is the one-month formulation of  
3 paliperidone palmitate.

4 Q. Do you have experience treating patients with Invega  
5 Sustenna?

6 A. We have quite a few patients currently on Invega Sustenna,  
7 yes.

8 Q. And Invega Trinza -- again, very briefly -- can you just  
9 tell us what Invega Trinza is?

10 A. It's the three-month formulation of paliperidone  
11 palmitate.

12 Q. And do you have any experience treating patients with  
13 Invega Trinza?

14 A. We have some patients that are currently on Trinza.

15 Q. Do you do any teaching related to second generation  
16 long-lasting antipsychotics, including Invega Sustenna and  
17 Invega Trinza?

18 A. Yeah, I've done national presentations on long-lasting  
19 injections. I've trained a pharmacy resident on long-acting  
20 injections, the pharmacokinetics and pharmacodynamics. And  
21 then we also teach the psychiatry residents on how to use  
22 long-acting injections.

23 Q. Prior to Invega Trinza coming to market, did you have any  
24 experience with a long-acting injectables antipsychotic that  
25 was dosed every three months?

1 A. There wasn't any prior to that, so no experience prior to  
2 Trinza.

3 Q. Excuse my interruption.

4 A. That's all right.

5 Q. Are there any others on the market today?

6 A. Not that I'm aware of.

7 Q. Does that three-month dosing interval impact patient care  
8 in any way?

9 A. Sure. You know, we talk about the advantage of one  
10 decision a month, one injection a month. That goes to four  
11 decisions a year, four injections a year. So, yes, some  
12 advantages for the patient and the system.

13 Q. Is adherence an issue for patients on Invega Trinza or on  
14 Invega Trinza?

15 A. Yes. We still see patients who miss doses. I mean, it's  
16 not a magic bullet for the compliance issue or adherence issue.

17 Q. Is adherence a choice?

18 A. Adherence can be a choice. Right? So the -- you know, as  
19 I talked about, there's lots of different reasons that  
20 patients, you know, stop taking their medicine. There's lots  
21 of different reasons that patients decide to stop taking their  
22 medicine or miss a dose. Could be they get incarcerated.  
23 That's not their decision necessarily. It could be that they  
24 become an inpatient and we screw up as health professionals.  
25 You know, we say it's supposed to be this day and then we don't

1 give it that day for whatever reason.

2 Q. If we could turn then, there's a document marked as  
3 Plaintiffs' Exhibit 1 in your book. It's the '693 patent. And  
4 I'd like to focus our attention on that for a moment.

5 Okay?

6 A. Sure.

7 Q. We can bring it up on the screen. All right.

8 Have you reviewed the '693 patent for purposes of  
9 providing expert testimony in this case?

10 A. I have.

11 Q. And for the record, when we're referring to the '693  
12 patent, is that Patent 10,143,693?

13 A. It is.

14 Q. Okay. So then just very generally, Dr. Sommi, what's the  
15 subject matter of the '693 patent?

16 A. So the '693 patent is instructions surrounding a dosing  
17 regimen for missed doses of long-acting paliperidone palmitate.  
18 And more specifically, the PP3M product.

19 Q. Does the '693 patent discuss the issue of adherence?

20 A. It does.

21 Q. And, Dr. Sommi, I should ask, did you help prepare some  
22 slides to assist with your testimony?

23 A. I did.

24 Q. And do you have the slide controls in your own hand?

25 A. I do.

1 A. Sure.

2 Q. Before you start, do these instructions have any  
3 significance to health care providers?

4 A. Yes. I mean, we look at them as guidance. It's the first  
5 place we look. If we don't know -- if you don't know if  
6 something is drug related or how do I dose this drug or what  
7 should I do, you turn first to the label because the company  
8 has as much information as anybody else about their drug. And  
9 if it's in the label, then that's where you start.

10 Q. If somebody misses a dose, what's one of the first things  
11 the health care professional will look to?

12 A. Well, if it's a dose of Invega Trinza, you would look to  
13 the label.

14 Q. Can we see how the Invega Trinza label matches up to claim  
15 5, if it does, of the '693 patent?

16 A. Sure.

17 You want me to run through it?

18 Q. Yes, please.

19 A. So this is a -- so the Claim 5 talks about a dosing  
20 regimen of paliperidone palmitate. So the label talks about  
21 dosing and administration, under number 2, of paliperidone  
22 palmitate. And this is a reinitiation dose. We're starting  
23 the patient back on the medicine. That's why it's called  
24 reinitiation.

25 In patients in need of treatment for schizophrenia,

1 psychosis, bipolar disorder, in the patent claim and in the  
2 Invega Trinza label, it talks about the indication for the  
3 treatment of schizophrenia, so directly consistent with  
4 schizophrenia in the claim.

5 And then it's for patients that have been treated  
6 with PP3M that were last administered an injection four to nine  
7 months ago in the claim.

8 And then in the missed dose section, it is doses -- a  
9 dose four to nine months since their last injection, so that's  
10 consistent both in the 2.3 wording, as well as in the table.

11 So the first step of the claim talks about  
12 administering in the deltoid, the first reinitiation dose of  
13 PP1M. And in the table, it talks about what happens on day  
14 one. So the patient comes in, this is what you're going to do  
15 on day one. And then it talks about, in the claim, what you  
16 should do between day four and day 12 with a PP1M deltoid  
17 injection. And in the label, it talks about day eight.  
18 There's another deltoid injection of Invega Sustenna, which is  
19 the one-month PP1M product. Day eight is exactly halfway  
20 between four and 12.

21 Then, finally, step three in the claim talks about  
22 administering a reinitiation dose of PP3M on the 23rd to 37th  
23 day. And in the label, it talks about administering Invega  
24 Trinza, which is the PP3M product, either in the deltoid or  
25 gluteal, one month after the second injection of the PP1M

1 product, and 30 days is about halfway between 23 and 37.

2 It goes on to talk about the missed dose. So the  
3 left-hand part of the claim is talking about what dose was  
4 missed of PP3M, and this was the what was the last dose of PP3M  
5 administered, right, of the Trinza and then you see something  
6 weird happen, you get the 175 and 273.

7 Q. Dr. Sommi, so the Claim 5 refers to 175 milligram  
8 equivalents, right?

9 A. Right.

10 Q. And the table in the Invega Trinza label talks about  
11 milligrams, 273 milligrams?

12 A. Right.

13 Q. Can you explain how they're related?

14 A. So there's different units, milligram equivalents versus  
15 milligrams, and this really has to do with the manufacturing  
16 process to a certain extent. I know you're really happy  
17 there's a molecule up on the screen.

18 This is what paliperidone looks like. In the  
19 manufacturing process, we esterify or we add this 16-chain  
20 palmitate ester. The importance of that is the molecule gets  
21 bigger. When the molecule gets bigger, it weighs more, so its  
22 molecular weight is larger. But it still only has one  
23 paliperidone molecule attached to it.

24 So then when we inject it into a patient, you have  
25 these enzymes called esterases that chop the ester back off and

1 let paliperidone be the molecule that runs around in the body.

2 So when we talk about milligram equivalence, the  
3 milligram equivalence table, you notice that there are -- that  
4 the dose or the amount, if you will, for paliperidone palmitate  
5 is bigger because of bigger molecules, so it takes more  
6 milligrams. So if I inject 273 milligrams of PP3, I get  
7 175 milligrams of paliperidone.

8 Does that make sense?

9 So when the drug products were approved, the FDA said  
10 "We want you to label these by the molecular weight of the  
11 paliperidone palmitate." So that's why there's this difference  
12 in these tables. So there's a conversion between paliperidone  
13 palmitate and paliperidone.

14 Q. Dr. Sommi, excuse me for interrupting.

15 Is that conversion set forth in the '693 patent  
16 anywhere?

17 A. Yes, it's in Table 3 of the '693 patent.

18 Q. Did you go back, then, to Claim 5 and compare it to the  
19 Invega Trinza label to see if the tables for dose amounts match  
20 up?

21 A. So if we convert in the Invega Trinza label all of the  
22 paliperidone palmitate milligrams to their milligram  
23 equivalents, highlighted here in blue, you see that the blue  
24 lines up exactly with the table in claim 5.

25 So Claim 5 has a missed dose of 175 milliequivalents



1 and in blue, 273 milligrams of PP3M delivers 175  
2 milliequivalents of paliperidone. The blue in here lines up  
3 perfectly with the table in claim 5.

4 Q. Just to be clear, because I'm not sure the blue is going  
5 to be part of the official record, do all of the dose amounts  
6 match up between the table in claim 5 in the '693 patent and  
7 the table 2 with the Invega Trinza label?

8 A. They do.

9 Q. Dr. Sommi, for Invega Trinza, who gives these injections?

10 A. All of the injections have to be given by a health care  
11 professional.

12 Q. Has the FDA approved self-administration?

13 A. No.

14 Q. If a health care professional was presented with a patient  
15 who was in need of treatment for schizophrenia, who had their  
16 last dose of PP3M four to nine months ago, and they followed  
17 the missed dose instructions in the Invega Trinza label, would  
18 they infringe the '693 patent?

19 A. If they followed Invega Trinza and gave Invega Trinza,  
20 would they infringe?

21 Q. Mm-hmm.

22 A. They would be following. I don't know that -- it's  
23 Janssen's product. I mean, I don't think they would be --

24 Q. Let me change the question a little bit.

25 A. Yeah.

1 Q. Let's say there could be infringement somehow. In other  
2 words, do they match up? Do the instructions in Invega  
3 Trinza's label instruct you to do each and every step in the  
4 same circumstances as Claim 5 of the '693 patent?

5 A. They do.

6 Q. If a patient then, if they miss a dose of PP3M four to  
7 nine months ago, and they come back into the clinic, who decide  
8 whether or not you're going to follow the missed dose regimen?

9 A. Their health care providers.

10 Q. Do you ever provide guidance to health care practitioners  
11 on what to do when a patient misses a dose of Invega Trinza?

12 A. With Invega Trinza, we start with the label. We follow  
13 it. So there's more than just this one guidance, but -- or  
14 instruction, but we follow the instructions. We try to figure  
15 out, well, when was the last dose given and what do we do. If  
16 there's something weird about that patient, then we do  
17 something different.

18 Q. Is it the exception or the rule that health care  
19 professionals would follow the missed dose instructions if a  
20 patient presented who had their last PP3M dose four to nine  
21 months ago?

22 A. I think most health care practitioners, at least that I  
23 work with, would start here and would end up following for most  
24 patients.

25 MS. MULLIN: So now if we can -- I'm going to put up,

1 with an injection four to nine months ago, and then the Mylan  
2 label includes the four to nine months since the last  
3 injection.

4 And then you have the three steps of the claim. The  
5 first step is the administration into the deltoid on day one of  
6 a PP1M product and then a second step of the claim is  
7 administration of a PP1M product on day eight in the Mylan  
8 label, similar to the Trinza label, and that is between the  
9 fourth and twelfth day.

10 Then the third step of the claim is the re-initiation  
11 dose of PP3M on or about the 23rd to 37th day, either deltoid  
12 or gluteal. And, again, you see the same thing one month after  
13 the second injection of the PP1M product.

14 Then the tables line up. And, again, if you put the  
15 milligram equivalents in there, you can see that the milligram  
16 equivalents in the Claim 5 are exactly the same as the  
17 milligrams of the PP1M and PP3M products.

18 Q. Did you do this analysis for all three of Mylan's proposed  
19 labels?

20 A. I did.

21 Do you want to hear all three the same way?

22 Q. For the record, yes, please.

23 A. Okay. Similarly, for the 350 milligram equivalent label,  
24 which is Plaintiffs' Exhibit 62, you can see the highlighting  
25 is exactly the same as the highlighting that I did for the

1 lower dose label. And then if you look at the label for the  
2 525-milligram, this is Plaintiffs' Exhibit 133, the  
3 highlighting, again, is exactly the same. There's no  
4 differences.

5 Q. Dr. Sommi, I think you said Plaintiffs' Exhibit 62.

6 Should that be 162?

7 A. It should be 162, yes.

8 Q. So you referred to highlighting.

9 Since highlighting might not be in the record, are  
10 you referring to a comparison between the patent Claim 5 and  
11 Mylan's proposed generic labels?

12 A. I am.

13 Q. Is the analysis the same for all three of Mylan's proposed  
14 labels with respect to the comparison to Claim 5?

15 A. Yes.

16 Q. So then in your opinion, Dr. Sommi, do Mylan's proposed  
17 label for all three of its ANDAs encourage, recommend or  
18 promote infringement of Claim 5?

19 A. Yes. So a health care professional would follow the  
20 guidance in Mylan's label and it aligns nicely with Claim 5 and  
21 so, yes, they would infringe.

22 Q. Is it inevitable that health care professionals will  
23 infringe Claim 5 of the '693 patent if they follow the missed  
24 dose instructions in Mylan's label?

25 A. Yes.

1 Q. Are there exceptions to that where people would not follow  
2 the missed dose instructions in Mylan's label?

3 A. Yes, certainly. There would be patients that don't, for  
4 whatever reason, fit or are somewhat different.

5 Q. Let me ask one more time, just to be clear.

6 In your opinion, do Mylan's proposed labels for those  
7 three ANDAs encourage, recommend or promote infringement of  
8 Claim 5?

9 A. Yes.

10 Q. Okay. We have some dependent claims as well that we've  
11 looked at, right, Dr. Sommi?

12 A. Sure.

13 Q. So referring to the '693 patent claims, 6 and 7, can you  
14 tell us what they describe and whether or not Mylan's label  
15 will induce infringement of those claims as well?

16 A. So Claims 6 and 7 refer to the diagnoses. So it's a  
17 method of Claim 5. This is the '693 patent, Claims 6 and 7,  
18 of Plaintiffs' Exhibit 1. This is where a patient is in need  
19 of treatment for psychosis, and Claim 7, in need of treatment  
20 for schizophrenia. And when you look at that in relationship  
21 to the proposed labels, you see that the indication is for the  
22 treatment of schizophrenia. So that lines up nicely with Claim  
23 7. And as we talked about earlier, schizophrenia is a --  
24 patients with schizophrenia have psychosis, so they would be in  
25 need of treatment for psychosis.

1 A. Yes, a health care professional following those  
2 instructions would infringe. That's right. So the labels  
3 would infringe.

4 Q. In your opinion, is it inevitable that Mylan's  
5 instructions will lead at least some health care professionals  
6 to infringe Claims 6, 7, 10, 11 and 14 of the '693 patent?

7 A. Yes.

8 Q. Do you have any doubt about that, Dr. Sommi?

9 A. I have no doubt.

10 Q. I'm going to ask one more time, Dr. Sommi, just so we make  
11 sure we got it.

12 In your opinion, do Mylan's proposed labels for its  
13 proposed ANDAs encourage, recommend or promote infringement of  
14 Claims 6, 7, 10, 11 and 14?

15 A. Yes.

16 Q. Dr. Sommi --

17 MS. MULLIN: I'm sorry, Your Honor, we don't have a  
18 copy of this for you, but we'll get you one.

19 Yesterday we received from Mylan a new submission to  
20 the FDA. We got this yesterday afternoon. I'll represent that  
21 to the Court and to you.

22 BY MS. MULLIN:

23 Q. Do you understand, Dr. Sommi, that there's a  
24 back-and-forth process between Mylan and the FDA where Mylan is  
25 seeking approval to market its generic PP3M products?

1 A. So I get approached. I talk with drug companies about  
2 ongoing work that they've got going, and we make an agreement.  
3 The university wants me to be engaged in clinical research,  
4 research in my area of research, and so they encourage me --  
5 with specific studies, they encourage me to do research.

6 Q. For those clinical studies, the universities received  
7 hundreds of thousands if not millions of dollars in  
8 compensation for the work you've done for Janssen, Alkermes,  
9 and others, correct?

10 A. Yes.

11 Q. You've also been a promotional speaker with respect to  
12 Invega Sustenna, correct?

13 A. I have.

14 Q. Do you know how much you've been paid for those  
15 promotional speaking engagements?

16 A. I couldn't tell you off the top of my head.

17 Q. You've never been involved in any studies or engaged in  
18 any capacity by a drug manufacturer with respect to a generic  
19 drug product, right?

20 A. I have not.

21 Q. Okay.

22 If we look at the '693 patent -- it's PTX1 in your  
23 earlier binder; it's DTX1 in the binder you have. We had hoped  
24 to have some joint exhibits to avoid this, but unfortunately,  
25 we weren't able to reach agreement on that. But other one,

1 approved by the FDA, correct?

2 A. Yes.

3 Q. Missed doses occur on exceptional occasions, according to  
4 Janssen, right?

5 A. It says, "To manage missed doses on exceptional occasions,  
6 then refer to 2.3."

7 Q. Right. So to manage missed doses on those exceptional  
8 occasions, right? That's what the label says?

9 A. That's what the label says.

10 Q. Okay. Let's go back to the '693 patent, DTX1.

11 You opine that it provides dosing regimens for  
12 reinitiating patients onto PP3M after missing a dose of PP3M  
13 depending on how much time has elapsed since the patient's last  
14 dose of PP3M, right?

15 A. Right.

16 Q. And you consider a patient to have missed a dose when they  
17 don't show up for their appointment, right?

18 A. Sure.

19 Q. A doctor that is aware of a patient missing a dose would  
20 encourage the patient to come get his or her shot as soon as  
21 possible, right?

22 A. That would be good practice.

23 Q. I think earlier today you mentioned that if you knew, you  
24 might go out and find them if they miss a dose?

25 A. Sure.



1 Q. So just to put this in perspective, first, a patient's  
2 diagnosed with schizophrenia, right?

3 I'm sorry I didn't hear an audible --

4 A. I'm sorry. Are you making this a step of the claim or --

5 Q. No, I'm just asking you generally.

6 So generally, the patient first is diagnosed with  
7 schizophrenia.

8 A. Patient comes in my practice, has schizophrenia.

9 Q. So you would diagnose the patient as having schizophrenia?

10 A. Sure.

11 Q. Then that patient is treated with PP3M.

12 A. Correct.

13 Q. For example, right?

14 A. Okay.

15 Q. To be treated with PP3M, a patient needs at least four  
16 months of PP1M, right?

17 A. Right.

18 Q. Then the question, at least for discussion today and we'll  
19 get into the claim as well, becomes whether that patient will  
20 be adherent or not, right?

21 A. Right.

22 Q. So let's actually look at the Asserted Claims.

23 MR. SODERSTROM: Scott, if we could pull up claim  
24 five. I think it's at DTX1.0. Yeah, perfect. And maybe if  
25 you can even extend it so that -- oh, you might have to pull it

1 from the next column with the chart as well.

2 BY MR. SODERSTROM:

3 Q. Let's just start with the basics here, Doctor.

4 If the patient does not miss a dose, there cannot be  
5 infringement of Claim 5, right?

6 A. No infringement.

7 Q. Even after missing a dose, if a patient does not return  
8 for treatment between four to nine months after his or her PP3M  
9 dose, there's no infringement, right?

10 A. No infringement.

11 Q. You'll agree with me -- and I think you may have testified  
12 to this, but I just want to be sure that I have it in the  
13 record -- but no health care provider is going to tell a  
14 patient to miss a dose, right?

15 A. Correct.

16 Q. And I think in your opinion, one of the single most  
17 important things health care professionals treating patients  
18 with schizophrenia can do is try to get them to stay on their  
19 medication, right?

20 A. Right.

21 Q. In your practice, you've never counseled a provider to  
22 tell a patient to miss a dose, right?

23 A. Well, so we tell patients to take a dose later if they've  
24 got side effects, for instance, in terms of managing potential  
25 consequences of getting the dose wrong. We may say well, come

1 in at four months or do whatever, but yeah, generally you don't  
2 tell people to miss a dose.

3 Q. Again, in your deposition you were far more unequivocal.  
4 You said "Yeah, no."

5 Is that right?

6 A. Yes.

7 Q. Let's say, though, that a patient does miss a dose and  
8 elects to come back between four to nine months. Okay?

9 Claim 5 then says to administer intramuscularly in  
10 the deltoid muscle of said patient a first reinitiation loading  
11 dose of PP1M, right?

12 A. Right. That's the first step of the claim.

13 Q. For the injections discussed in Claim 5, a patient cannot  
14 self-administer those, right?

15 A. Correct.

16 Q. So that administration would be done by someone other than  
17 a patient, a health care provider?

18 A. Well, it would be a health care provider, yes. Right.

19 Q. And then this patient that has shown he or she was prone  
20 to nonadherence or certainly has missed a dose needs to come  
21 back four to 12 days later for another shot under the second  
22 administration limitation, right?

23 A. Right. So we would schedule the patient to come in a week  
24 later for that second dose.

25 Q. And that patient has to show up between four and 12 days,

1 right?

2 A. Correct.

3 Q. If the patient doesn't show up between four to 12 days for  
4 the second administration, there can be no infringement, right?

5 A. No infringement.

6 Q. As you previously put it, the patient has to return for  
7 that second injection to get most of the way there for  
8 infringement, right?

9 A. Ask the question again.

10 Q. Sure.

11 As you previously testified, the patient has to  
12 return for that second injection to get most of the way there  
13 for infringement, right?

14 A. Okay.

15 Q. Is that right?

16 A. Yes.

17 Q. If the patient does show up and is administered a second  
18 reinitiation loading dose of PP1M, then that same patient who  
19 did not adhere at first would need to show up again 23 to 37  
20 days later for a reinitiation dose of PP3M, right?

21 A. That's the third step of the claim that would require that  
22 third dose to be administered 23 to -- on the 23rd or 37th day  
23 after the second reinitiation loading dose. Right.

24 Q. Just to make sure I have it right, that same patient who  
25 did not adhere -- that's why we're here in the first place --

1 did not adhere, would need to show up again 23 to 37 days later  
2 for a reinitiation dose of PP3M, right?

3 A. That's correct.

4 Q. So it's the patient that perhaps is prone to missing doses  
5 that has to show up multiple times after the first dose under  
6 Claim 5, right?

7 A. Well, it doesn't say anything about missing multiple  
8 doses.

9 Q. I'm sorry. Missed a dose. I can rephrase it. At least  
10 one dose.

11 So it's a patient that perhaps is prone to missing a  
12 dose that has to show up multiple times after the first dose  
13 under Claim 5, right?

14 A. Well, the patient could have missed a dose for a lot of  
15 different reasons. Could have been they got incarcerated,  
16 could have been they were traveling, could have been they -- we  
17 scheduled it incorrectly. It could have been a lot of  
18 different reasons why the patient missed the dose.

19 What the claim says is if you're faced with a  
20 situation where a patient shows up and the last dose that they  
21 were given was four to nine months ago, then you do those three  
22 things.

23 MR. SODERSTROM: Scott, can you pull up from the  
24 transcript page 101, lines four through seven?

25

1 BY MR. SODERSTROM:

2 Q. Dr. Sommi, at your deposition, I asked you, "So it's the  
3 patient that perhaps is prone to missing doses, has to show up  
4 a bunch of times after that first dose, right?"

5 You answered, "Correct."

6 That was the question I asked and the answer you  
7 provided, right?

8 A. Right.

9 MR. SODERSTROM: Now, if we look back at the claim,  
10 Scott.

11 BY MR. SODERSTROM:

12 Q. If we look at part two, if the patient missed a dose and  
13 then came back between four to nine months for their first  
14 injection but then missed the second reinitiation dose, is  
15 there a separate dosing regimen for that person?

16 A. So is your question what do you do with that person then?

17 Q. It's actually more simple. It's just is there a separate  
18 dosing regimen for a person that came back on day one but then  
19 missed the second reinitiation loading dose?

20 A. No.

21 Q. That's just something that a clinician would be able to  
22 deal with, right?

23 A. That would be the situation we would face, right.

24 Q. That's because Claim 5 really deals with that patient who  
25 misses between four to nine months and returns for all three

1 patient misses a dose and shows up a day after nine months  
2 since his or her last dose, right?

3 A. Correct.

4 Q. So we've discussed a number of different situations, and  
5 you'll agree with me that to infringe Claim 5, the patient  
6 would have to miss a dose between four and nine months after  
7 their last dose, receive the three injections guided by the  
8 table of their previous dose, right?

9 A. Right.

10 MR. SODERSTROM: Scott, can we pull up Plaintiffs'  
11 slide five from the Sommi slides?

12 BY MR. SODERSTROM:

13 Q. This is one of the slides that you created and walked  
14 through earlier, right?

15 A. Right.

16 Q. I just want to make sure that at least I understand that  
17 based on the testimony you just gave, if a patient misses a  
18 dose, there can be -- I'm sorry.

19 If a patient does not miss a dose, there can be no  
20 infringement of Claim 5, right?

21 A. Correct.

22 Q. If a patient does not return for treatment between four to  
23 nine months since last injection, there can be no infringement,  
24 right?

25 A. Correct.

1 Q. If a patient does return between four to nine months since  
2 the last injection, but does not return for treatment on about  
3 the fourth day to about 12th day after first reinitiation  
4 loading dose, no infringement, right?

5 A. Right.

6 Q. If a patient returns for treatment between four to nine  
7 months, gets the first loading dose, gets the second  
8 reinitiation loading dose between the fourth and 12th day but  
9 does not return for treatment on about the 23rd day to about  
10 the 37th day after first reinitiation loading dose, there's no  
11 infringement of Claim 5, right?

12 A. Correct.

13 Q. That's just based on the standard language that's used in  
14 claim five in determining infringement, right?

15 A. So the language is if they don't get the first, second, or  
16 third doses according to the schedule and they haven't  
17 missed -- they don't fit the profile of the patient, then --  
18 and the health care provider doesn't follow the instructions as  
19 listed there, steps one, two, three, they don't do any one of  
20 those things. If the patient is not that patient, then they  
21 don't infringe. It's pretty straightforward.

22 Q. I agree.

23 In this case, you have not provided any records of  
24 any patients actually missing a dose or showing back up between  
25 four and nine months after their last dose and receiving the



1 three injections as provided in claim five, right?

2 A. That would be a HIPAA violation, actually.

3 Q. To be clear, we haven't gone through any hurdles to be  
4 able to prove that here. You have not shown any evidence,  
5 correct?

6 A. Correct.

7 Q. And you have no idea what percentage of patients that miss  
8 their dose return for treatment four to nine months after their  
9 last dose of PP3M, right?

10 A. No, I have not.

11 Q. But the doctor will know about the patient missing a dose  
12 when the patient doesn't show up for his or her appointment,  
13 right?

14 A. So physicians have access to the medical record. They can  
15 look up when the last injection was given.

16 Q. So the doctor will know if the patient misses an  
17 appointment?

18 A. When the patient doesn't show up for their appointments,  
19 then that's a pretty good indication that they're going to miss  
20 a dose.

21 Q. And the doctor would want to get the patient back on his  
22 or her treatment as soon as possible, right?

23 A. Correct.

24 Q. You've never administered Invega Sustenna, correct?

25 A. I have not.

1 A. Okay.

2 Q. And, again, much like what we just looked at here, the  
3 information provides under administration instructions that  
4 "Paliperidone palmitate extended-release injectable suspension  
5 should be administered once every three months."

6 Right?

7 A. That's what it says.

8 Q. And if we look just above that, in the indications and  
9 usage section, do you see where it says that "Extended-release  
10 paliperidone palmitate is indicated for treatment of  
11 schizophrenia in patients after being treated with one month  
12 paliperidone palmitate PP1M for at least four months"?

13 Right?

14 A. Correct.

15 Q. There's nothing in this indication and usage section that  
16 talks about missed doses, right?

17 A. There is nothing there.

18 Q. And so given that the indications and usage section says  
19 nothing about a missed dose and Claim 5 is directed to a missed  
20 dose, there can be no infringement based solely on the  
21 indications and usage section of the label, right?

22 A. Right.

23 Q. Instead, the indication requires that the patient has been  
24 adequately treated with PP1M for at least four months, right?

25 A. That's what the indications and usage section says.

1 A. They often do, yes.

2 Q. They need to, right?

3 A. Yeah, they need to.

4 Q. Now, you've opined in this case that no matter what,  
5 regardless of a patient's condition, you're going to start by  
6 following the prescribing information, right?

7 A. Right.

8 Q. You were engaged by Janssen as an expert in this matter  
9 sometime in 2021; is that right?

10 A. A little over a year ago, yeah.

11 Q. In April of 2018, you gave a presentation in Indianapolis  
12 titled "Examining the pharmacokinetics and pharmacodynamics of  
13 long-acting injectable antipsychotics, How to best  
14 individualize treatment."

15 Right?

16 A. I did.

17 Q. And you're aware that that presentation was posted on the  
18 Internet at powerpak.com in May of 2018, right?

19 A. I am.

20 Q. Let's take a look at DTX-214.

21 These are the slides that you used for that  
22 presentation; is that correct?

23 A. They appear to be.

24 Q. I'm sorry?

25 A. They appear to be.

1 Q. And the audience for this presentation was a group of  
2 pharmacists like yourself who practice primarily or exclusively  
3 in psychiatric studies, right?

4 A. Correct.

5 Q. One of the slides at DTX-214.0045 has a quick case  
6 summary.

7 You created this slide, correct?

8 A. I did.

9 Q. It says that a patient missed a dose of a once-a-month LAI  
10 and says "What should you do?"

11 Right?

12 A. That's what it says, yes.

13 Q. And on the next slide, you ask the audience "What would  
14 you do?" with five possible options: Restabilize her on oral  
15 meds, then switch back to LAI; give her an injection of her  
16 usual dose plus oral overlap; give her a higher dose of her  
17 usual LAI antipsychotic; switch LAI antipsychotics; or unsure.

18 Right?

19 A. Yes. This is an audience response question just to gauge  
20 what they would do.

21 Q. Right.

22 But here, you did not say to always start by  
23 following the prescribing information, right?

24 A. That wasn't the intent of the question.

25 Q. That wasn't even an option you suggested to this group of

1 pharmacists in 2018, was it?

2 A. Right. Well, this is a teaching technique.

3 Q. So you would not teach them to follow the --

4 A. No --

5 Q. -- prescribing information?

6 A. That's not what I said. This is a teaching technique  
7 where you ask the audience what they would do and then you can  
8 talk about the answers that they gave.

9 Q. And after polling the audience, your statement to the  
10 attendees about what a health care provider should do is that  
11 any one of those options is good, right?

12 A. I don't know. You listened to it. So I'm sure if that's  
13 what I said, that's what I said.

14 I'm sorry you had to listen to the whole thing to get  
15 to there.

16 Q. I've spent hours of my life doing worse things.

17 So at least in 2018, you are not saying that no  
18 matter what, regardless of a patient's condition, you're just  
19 going to start by following the prescribing information, right?

20 A. Right. So I'm not -- so, again, if you go back to the  
21 previous slide, I'm not talking about any specific drug.

22 Right? So that's why there isn't anything specific.

23 Q. Well --

24 A. These are all of the options for all of the long-acting  
25 injections.

1 Q. But when you were talking about specific drugs and  
2 packages, you said the problem with package inserts is that  
3 they do not consider what the patient looks like and that's a  
4 problem, right?

5 A. I did.

6 Q. And that's why, despite telling me that no matter what,  
7 you'll start with the label, in reality -- and as you told me  
8 at your deposition -- whether to reinitiate is actually a  
9 decision by the health care provider, depending on the status  
10 of the patient.

11 Right?

12 A. That's right. The health care provider makes that  
13 decision.

14 Q. And you're aware that as of 2018, Trinza had been on the  
15 market for roughly three years, correct?

16 A. Okay.

17 MR. SODERSTROM: Thank you, Doctor.

18 THE WITNESS: Sure.

19 MS. MULLIN: Shouldn't be more than an hour and a  
20 half, Dr. Sommi. Just kidding.

21 (REDIRECT EXAMINATION)

22 BY MS. MULLIN:

23 Q. Okay. Is Mylan's generic product on the market?

24 A. It is not.

25 Q. Have you seen any commercial advertisement, websites, or

REDIRECT - R. SOMMI, M.D. - MULLIN

148

1 THE COURT: I'll allow it.

2 MS. MULLIN: Thank you.

3 BY MS. MULLIN:

4 Q. In your opinion, Dr. Sommi, will each of Mylan's proposed  
5 labels inevitably lead some health care professionals to  
6 infringe the Asserted Claims for the '693 patent?

7 A. Yes.

8 MS. MULLIN: At this point, I would just like to move  
9 for admission of some exhibits. During his testimony,  
10 Dr. Sommi referred to -- and I can ask -- can the Court excuse  
11 the witness?

12 THE COURT: Yes, we're done with you. You're  
13 excused.

14 MS. MULLIN: He'll be back.

15 (Witness excused.)

16 MS. MULLIN: I would like to move for admission of  
17 Plaintiffs' Exhibit 1, which is the '693 patent, Plaintiffs'  
18 Exhibit 43, Plaintiffs' Exhibit 92, Plaintiffs' Exhibit 133,  
19 Plaintiffs' Exhibit 162 and Plaintiffs' Exhibit 128A, as well  
20 as -- we'll have to get you an exhibit-marked copy of  
21 Plaintiffs' Exhibit 595, which is the document that was  
22 produced yesterday.

23 I'd also like to move for admission of Plaintiffs'  
24 Exhibit 2, Plaintiffs' Exhibit 3, and Plaintiffs' Exhibit 4,  
25 which relate to the stipulation on ownership.

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

CIVIL ACTION NUMBER:

Plaintiffs,

2:20-cv-13013-EP-LHG

vs.

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

BENCH TRIAL VOL. 2

Defendants.

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
November 30, 2022  
Commencing at 10:00 a.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
UNITED STATES DISTRICT JUDGE**



1 professional work experiences?

2 A. Yes, it does.

3 Q. All right. So let's go through some of those experiences.

4 What is your highest level of education?

5 A. Medical doctor, University of Michigan, 1972.

6 Q. Dr. Berger, you received your medical degree in 1972; is  
7 that correct?

8 A. Yes.

9 Q. And as a medical doctor, do you have a field of specialty?

10 A. Yes. My field of specialty within medicine is psychiatry,  
11 subspecialty is forensic psychiatry, and my area of expertise  
12 is schizophrenia. Over my career, about half of my patients  
13 have carried a diagnosis of schizophrenia.

14 Q. So I'm going to ask you a little bit about those patients  
15 that you've treated with schizophrenia and specifically what  
16 you just testified to, about half of your patients being  
17 afflicted with schizophrenia.

18 Before I do, do you consider yourself to be a  
19 practicing psychiatrist?

20 A. Well, I am a practicing psychiatrist. I introduce myself  
21 as a medication manager, yes.

22 Q. And how long have you been a practicing psychiatrist?

23 A. Fifty years and two months.

24 Q. That's a fairly impressive amount of time.

25 If you don't mind me asking, what motivates you to

1 earlier, that about half of the patients you've seen or treated  
2 over your career have been afflicted with schizophrenia.

3 Do you recall that?

4 A. Yes.

5 Q. Okay. And if we were to put a number for the Court to how  
6 many unique patients you've seen or treated that have been  
7 afflicted with schizophrenia, what would that be?

8 And let me put a caveat to that question to you.

9 What I mean by unique patients is just unique  
10 patients that you are seeing and then treating for the first  
11 time. I'm not including patients that you might be seeing on a  
12 recurring basis. How many would you say that would be?

13 A. I'd estimate about 10,000 unique psychiatric patients over  
14 my career.

15 Q. And in your treatment of those patients, do you prescribe  
16 medications?

17 A. Yes, I do. As I said, I call myself a medication manager.

18 Q. So then bringing the issues a little bit closer to what  
19 this case entails, do you have any experience prescribing  
20 paliperidone palmitate?

21 A. Yes, a lot.

22 Q. Do you have any experience prescribing Invega Sustenna?

23 A. Yes, a lot of experience.

24 Q. So since you've prescribed Invega Sustenna, could you just  
25 briefly describe in your own words, what is Invega Sustenna?

1 A. Sure. Invega Sustenna is a medication used to treat  
2 schizophrenia. It's a long-acting injection intended to last  
3 about a month. It's a monthly treatment for schizophrenia.

4 Q. Is it a paliperidone palmitate formulation?

5 A. Yes, it is.

6 Q. Okay. And really bringing it to the issues of this case,  
7 do you have any experience with prescribing Invega Trinza?

8 A. Yes, I have experience with that also.

9 Q. You've actually prescribed Invega Trinza?

10 A. A lot of times, yes.

11 Q. Okay. So the same question.

12 If you could briefly just explain, what is Invega  
13 Trinza in your own words?

14 A. It's the three-month equivalent of Invega Sustenna, the  
15 one-month preparation.

16 Q. So we're going to talk at some point about just  
17 prescribing informations in general, but without putting  
18 anything up, do you know what Invega Trinza is actually  
19 indicated for?

20 A. Yes. It's indicated for the treatment of schizophrenia.

21 Q. And Invega Trinza is also a paliperidone palmitate  
22 formulation; is that correct?

23 A. Yes.

24 Q. Okay. Just so the record is clear then, what is the  
25 difference between Sustenna and Trinza?

1 would be called a change in the treatment plan and the health  
2 care professional doesn't have control over that anyway.

3 Point B, there are two places in the package insert  
4 that say missed doses should be avoided. That's the exact  
5 opposite of encouraging a patient to miss a dose. It  
6 encourages the patient to stay on the dose, get the dose at the  
7 scheduled times.

8 The fourth point, standard of care, is an important  
9 one to me as a prescribing physician. Standard of care drives  
10 treatment decisions; the package insert does not. The  
11 physician is required to examine the patient and determine,  
12 according to the standard of care, the treatment that's  
13 indicated for that patient at that time. That decision is  
14 driven by the standard of care, not by the label.

15 Q. All right. Thank you for that, Dr. Berger.

16 You said prescribing information.

17 Is that sometimes referred to as the label?

18 A. Yes.

19 Q. Okay. So if I use prescribing information or label  
20 interchangeably, will you understand what I'm referring to?

21 A. Yes.

22 Q. Okay. All right.

23 So you just summarized your opinions, and I  
24 appreciate that. And before we go into, though, the details of  
25 those opinions, I want to do a little bit of background on just

1 schizophrenia itself, much like what plaintiffs' expert did as  
2 well.

3 What is schizophrenia?

4 And with that, why don't we go to your slide two.

5 A. Schizophrenia is a serious mental illness. It affects  
6 about 1% of the world's population, commonly starts before age  
7 25, and once it starts, it's there for the rest of the person's  
8 life.

9 Q. And does schizophrenia impact patients' lives, or those  
10 patients that are afflicted with schizophrenia?

11 A. Yes, a huge impact. Ordinarily, people with schizophrenia  
12 function at a lower level than the people in society who don't  
13 have schizophrenia. It's common for schizophrenics to be  
14 unemployed because they don't have the mental stability to hold  
15 down employment and, therefore, they're usually in poverty,  
16 often homeless. They usually live either with relatives or in  
17 a group home or even at a homeless shelter, and sometimes under  
18 a bridge. They're often in jail or prison because their  
19 behavior gets them in trouble. And, unfortunately, they also  
20 often die by suicide. About 10% of schizophrenic patients die  
21 by suicide.

22 Q. Yes, it is indeed a tragic affliction.

23 What about psychosis? Because I think during this  
24 trial, the term psychosis, at least, will be battered around.  
25 What does psychosis refer to?

1 A. Psychosis is loss of contact with reality. It's commonly  
2 manifested as hallucinations like hearing things that are not  
3 there or having ideas, thinking that things are happening when  
4 they're not happening. Like the aliens are listening in on my  
5 thoughts.

6 Q. Is there any relationship between psychosis and  
7 schizophrenia?

8 A. Yes. Schizophrenia is a type of psychosis.

9 Q. So then keeping the focus just on schizophrenia, is there  
10 currently a cure for schizophrenia?

11 A. No, no cure.

12 Q. So if there's no cure for schizophrenia, is schizophrenia  
13 at least treatable?

14 A. Well, yes. And that's the purpose of all these  
15 medications, to treat schizophrenia, to reduce the symptoms or  
16 hopefully eliminate the symptoms so that a person can live a  
17 more normal life than without medications.

18 Q. So you mentioned medications.

19 What type of medications are used to treat  
20 schizophrenia?

21 A. A group of medications called antipsychotic medications.

22 Q. And that treatment with medications, is that the same for  
23 any and all patients that are afflicted with schizophrenia?

24 A. No. Each patient is unique. Each patient has his own  
25 symptoms, his own situation. For instance, is he homeless or

1 does he live with relatives. Each patient has his own response  
2 to treatment, how much the medication reduces the symptoms.  
3 Each patient has his own set of side effects, and side effects  
4 can be either desirable side effects or undesirable side  
5 effects.

6 Q. Thank you, Dr. Berger. Let's go to slide three.

7 So I see a lot there on that slide, Dr. Berger, and  
8 I'm not even going to pretend to try to decipher that. So what  
9 are you trying to show the court with this slide?

10 A. This slide shows a progression of the development and use  
11 of antipsychotic medication. It starts on the left with  
12 Thorazine chlorpromazine in 1952, first as a tablet and then it  
13 and the other medications are gradually introduced, started as  
14 tablets, and then became liquids, and then become introduced as  
15 short-acting injectable medications, and then long-acting  
16 injectable medications. So those are the blue ones on the left  
17 side of the screen.

18 The green ones on the right side of the screen called  
19 second generation or atypical antipsychotic medications began  
20 in 1988 with clozapine and Clozaril. Again, it started with  
21 pills, and then liquids, and then short-acting injections, and  
22 then long-acting injections. And as you can see, a lot of them  
23 were introduced after clozapine in 1988.

24 Q. And so bringing it to the particular drug at issue here,  
25 Invega Trinza, is Invega Trinza an antipsychotic medication?

1 opinions?

2 A. Yes.

3 Q. Okay.

4 Did anybody else rely on this article?

5 A. Yes, I noticed that Dr. Sommi referenced this article in  
6 his opening report.

7 Q. So plaintiff's infringement expert relied on this article  
8 as well?

9 A. Yes.

10 Q. Okay. And to your knowledge, though, did Dr. Sommi opine  
11 in any way about patients making a conscious decision to not  
12 comply with their medication regimen?

13 A. I saw nothing about that in Dr. Sommi's testimony or his  
14 report.

15 Q. You talked about nonadherence and compliance.

16 Is patient nonadherence still a problem today?

17 A. Yes, a big problem.

18 Q. You said that you have no issues with the drug Trinza,  
19 correct?

20 A. Yes, that's correct.

21 Q. Has Trinza solved issues of patient nonadherence?

22 A. No. It's still a problem, still a big problem.

23 Q. So then, bringing it to the patent, let me ask you this --  
24 and it might sound like a bit of an odd question -- but does  
25 the phenomenon of patient nonadherence still occur despite the



1 Q. Okay. I see to the right of the claim, you have a number  
2 of text boxes, correct?

3 A. Yes.

4 Q. Okay.

5 You have also done that color coding or that color  
6 designation with those text boxes, yellow and the lighter shade  
7 of blue?

8 A. Yes.

9 Q. Okay.

10 What are you signifying there in those text boxes to  
11 the right of the claim?

12 A. Those are the parts of the claim that correlate to the  
13 seven boxes I have on the right.

14 Q. Got it.

15 So, do you mind then just walking through those text  
16 boxes for the Court and keeping in mind your color coding  
17 itself and what that signifies?

18 A. Sure. So the first box says miss a dose. The patient  
19 does that. The patient does that on his own volition without  
20 any input from the health care professional. He misses it  
21 either because he forgets or because he decides not to do it.  
22 Then the second box shows that then the patient desires to  
23 resume treatment, desires to continue treatment, and indeed  
24 comes back in to continue treatment exactly four to nine months  
25 after the last dose of -- the last dose of PP3M.

1 Q. Okay.

2 So underneath that now, now we see the lighter shade  
3 of blue text box.

4 What are you signifying there?

5 A. That's what's done by the health care professional. So  
6 when the patient comes back in after four to nine months, the  
7 health care professional then does something. He examines the  
8 patient, determines according to the standard of care the  
9 indicated treatment, and treats the patient. According to this  
10 regimen, he treats the patient with a dose of PP1M,  
11 reinitiation loading dose.

12 Q. Okay. And underneath that again, you have a yellow text  
13 box. Same question again, more recordkeeping exercise.

14 What are you signifying there?

15 A. The next yellow box is the next thing the patient does.  
16 After that first office visit, then the patient comes back in  
17 four to 12 days later, again, because the patient decides to of  
18 his own accord, no input from the health care professional, he  
19 comes back in. That's the patient action.

20 Q. Then that follows another text box that's in the lighter  
21 shade of blue, correct?

22 A. Correct.

23 Q. And you're signifying what there?

24 A. So when the patient comes back in after four to 12 days,  
25 the health care professional does the same thing, evaluates the

1 patient, determines according to the standard of care the  
2 indicating treatment, and provides treatment. According to  
3 this regimen, that treatment is the second reinitiation loading  
4 dose of PP1M.

5 Q. So keeping with the exercise that we've just engaged in  
6 then, what does the text box that follow, what does that  
7 signify?

8 A. Next is the third yellow box. So after that, the next  
9 thing that happens is the patient decides of his own accord to  
10 come back in 23 to 37 days later of his own accord, meaning  
11 also of his own decision. It's his action. The health care  
12 professional doesn't do that; the patient does that. The  
13 patient comes back in.

14 Q. To round it out then, the final text box that's in the  
15 shade of blue, what are you signifying there?

16 A. The last blue box, the patient then -- the health care  
17 professional then does the same thing. He examines the  
18 patient, treats the patient according to the standard of care,  
19 and in this regimen, that means administering a dose of PP3M.

20 Q. All right.

21 So, let me ask you this question -- and truthfully,  
22 Dr. Berger, you may be asked this question on cross, but even  
23 for my purposes I'd like to know.

24 You have in that first text box miss a dose.

25 Where in the claim does it say miss a dose?

1 A. In the text on the left, the first yellow highlighted  
2 section that says wherein said patient had been last  
3 administered a PP3M injection four to nine months ago. It says  
4 the patient was administered the medication, the patient was  
5 supposed to get the medication, and he didn't. Why didn't he?  
6 Because the patient missed the dose. Patient action; patient  
7 missed the dose.

8 Q. And PP3M is a three-month formulation; is that correct?

9 A. Yes, as I said earlier.

10 Q. All right. So Dr. Berger, on this slide itself, you just  
11 walked us through several steps that you've outlined there.  
12 I'm going to confront a criticism that plaintiffs had.

13 Did you rewrite any of the language of Claim 5 to  
14 arrive at your opinion regarding those steps?

15 A. No.

16 Q. Now, Dr. Berger, you've read Dr. Sommi's trial testimony,  
17 correct?

18 A. Yes.

19 Q. Dr. Sommi says that that limitation that you've  
20 highlighted there in the yellow on the claim -- so I'm just  
21 focused on that first yellow highlight of the claim -- that  
22 says wherein said patient had been last administered a PP3M  
23 injection four to nine months ago.

24 Do you see that?

25 A. Yes.

1 Q. Okay. So Dr. Sommi says that that very same limitation,  
2 the one that you highlighted there, well, that's not a step,  
3 that's not an action that anyone does. That's simply a -- I'm  
4 sorry. I'm going to quote it -- "a descriptor of the clinical  
5 situation."

6 Do you agree with that opinion?

7 A. No, I do not agree with that opinion.

8 Q. Why not?

9 A. What Dr. Sommi is describing is that the patient has  
10 schizophrenia. The patient doesn't choose to have  
11 schizophrenia. He doesn't decide to have schizophrenia. He  
12 doesn't go to the store and pick out schizophrenia to put on,  
13 like, a jacket. It's something that happens. It happens to  
14 him. He's the victim of schizophrenia.

15 This claim says the patient misses the dose. The  
16 patient is already on the medication; he misses his next dose;  
17 that's the something the patient does. The patient decides to  
18 do or it happens because the patient does something else. He  
19 forgets to do it. It's patient action, patient decision, and  
20 entirely within the patient's control.

21 Having schizophrenia isn't within his control.  
22 Missing the dose is within his control.

23 Q. To your knowledge, has Dr. Sommi ever treated a patient  
24 with schizophrenia?

25 A. Well, Dr. Sommi is a pharmacist. He doesn't treat

1 patients.

2 Q. Since we're talking about actions of two actors, can PP3M  
3 be self-administered? In other words, can the patient just do  
4 it him or herself?

5 A. No, this medication is not intended to be  
6 self-administered.

7 Q. So Dr. Berger, I'm going to pose a hypothetical to you.

8 All right?

9 Say I had a claim -- and assume right now for my  
10 hypothetical purposes, don't worry about the specification,  
11 don't worry about anything there, okay? Just isolate it to a  
12 claim -- say the claim said a method for treating  
13 schizophrenia by administering a therapeutically effective  
14 amount of PP3M. Say it stopped right there.

15 In your opinion, if that was the claim -- and be it  
16 as it may, that's not the real world, but I'm posing this  
17 hypothetical -- if the claim stopped right there, would your  
18 opinion be that that claim called for patient action?

19 A. No. What you described calls for action on the part of  
20 the health care professional. It says what the health care  
21 professional does, not what the patient does.

22 Q. All right. Thank you for that, Dr. Berger.

23 With respect to your opinion here, though, regarding  
24 the claim requiring two actors, is that opinion supported  
25 elsewhere in the patent?

1 Q. And by how far would the Michigan player be outside the  
2 window?

3 A. One day outside the window.

4 Q. Let's move on to now the Michigan State guy, patient B.  
5 What are you showing regarding patient B?

6 A. Patient B is an identical patient, but he comes back for  
7 his injection exactly four months after the last injection.

8 Q. So now, would patient B actually fall within the four to  
9 nine month missed dose window of the Asserted Claims?

10 A. Yes, he does.

11 Q. Okay. Now, you mentioned that patient B and patient A are  
12 identical. By that, do you mean the clinical considerations  
13 with respect to those patients?

14 A. Yes.

15 Q. Okay. So I want to know clinically speaking what you  
16 would do for each of these patients? And again, assuming then  
17 they present identical clinical considerations, except for the  
18 fact that patient A came one day before and patient B came one  
19 day later. How would you treat patient A and B? These  
20 patients, they're identical in every respect, except for the  
21 fact that A came one day before.

22 A. I would treat them -- as a psychiatrist with over 50  
23 years' experience, I would treat them -- assuming that the  
24 standard of care indicates they should stay on paliperidone  
25 palmitate -- I would treat them both with PP3M injections.

1 Q. So then if I'm understanding that correctly, you would --  
2 regardless of the fact that they're one day apart, you would  
3 prescribe both patient A and B the previously missed dose of  
4 PP3M?

5 A. That's correct. I have slides that illustrate this  
6 analogy.

7 Q. We can get into that.

8 Again, you would do that despite the fact that  
9 there's this one-day disparity between the two patients.

10 Is that correct?

11 A. Yes.

12 Q. Why?

13 A. Both patients have proven themselves to be nonadherent.  
14 They both have shown that they don't come back for their doses  
15 when they're supposed to. It is wiser and safer to treat them  
16 both with a medication that protects them from the symptoms of  
17 schizophrenia for three months than to treat them with a  
18 medication that protects them for only one month. That's why.

19 Q. So would you ever consider or take into account what the  
20 patient's response is to the medication prior to coming back?

21 A. Well, sure. And that's required by the standard of care.  
22 The health care professional has to evaluate the patient, and  
23 that includes evaluating the reason why the dose was missed in  
24 the first place.

25 Should I give examples or go on?



1 Q. No, I think that's fine.

2 Let me ask you this question because I think you've  
3 outlined your position there.

4 We're going to talk a lot about the prescribing  
5 information on the label when it comes to your opinions  
6 regarding specific intent.

7 In connection, though, with your opinions here at  
8 this time on the divided infringement issue, have you reviewed  
9 the prescribing information for Invega Trinza?

10 A. Yes.

11 Q. Okay. And had you actually reviewed that prescribing  
12 information even prior to your participation in this particular  
13 matter?

14 A. Yes, of course.

15 Q. So keeping with that clinical hypothetical that we were  
16 talking about, the patients being one day apart, and that's  
17 part of the reason I wanted to move into this particular part.

18 If a provider were to blindly follow the prescribing  
19 information for the Invega Trinza, how would that prescriber  
20 treat patient A and patient B? How would those patients be  
21 reinitiated if the practitioner were to just blindly follow the  
22 label, again, keeping with the hypothetical that these patients  
23 are one day apart?

24 A. So the animated slide shows this. Patient A would be  
25 treated with an injection of PP3M. Patient B would be treated

1 Scott, I'd like to point Dr. Berger to Section 1.

2 BY MR. MUKERJEE:

3 Q. Dr. Berger, I have Section 1 blown up.

4 What is Section 1 in Mylan's proposed prescribing  
5 information?

6 A. It's the section of the prescribing information that  
7 describes the indications and usage of Mylan's ANDA products.

8 Q. Have you reviewed this section in its entirety?

9 A. Yes.

10 Q. Is this the actual indication that the drug would be  
11 marketed for?

12 A. Yes, the treatment of schizophrenia.

13 Q. In your opinion, does this section -- the section that  
14 outlines what the drug is actually indicated for and how it'll  
15 be used -- does that infringe upon or do any of the indications  
16 that are set forth here infringe upon Claim 5?

17 A. No, they do not infringe.

18 MR. MUKERJEE: Your Honor, for my oft praise of  
19 recordkeeping exercises, I'm going to try to keep the  
20 examination limited to Claim 5 because that is, of course, the  
21 independent claim.

22 As Dr. Berger has testified to, the other Asserted  
23 Claims all depend from Claim 5. So whatever limitations there  
24 are there flow through to the Dependent Claims.

25 BY MR. MUKERJEE:

1 yes.

2 Q. Okay.

3 So then is it fair to say prior to being initiated on  
4 PP3M, a patient had to at least have four monthly doses of  
5 PP1M?

6 A. That's the common practice, yes.

7 Q. In your professional opinion, in your clinical opinion, if  
8 a patient is non-adherent on PP3M, does it make sense to switch  
9 a patient back to a medication they previously adhered to,  
10 PP1M?

11 A. Yes, that makes sense.

12 Q. Let's go to Section 2.17.

13 Dr. Berger, I think you know my -- my mantra now.

14 Have you reviewed Section 2.7?

15 A. Yes.

16 Q. What is Section 2.7?

17 A. It's a section of a label that describes switching a  
18 patient from PP3M to Invega -- to paliperidone tablets.

19 Q. Paliperidone tablets.

20 So a patient is on PP3M. This section deals with  
21 then switching that patient from the long-acting depot  
22 injection of paliperidone palmitate to now an oral tablet  
23 formulation; is that correct?

24 A. Yes.

25 Q. With the use of Mylan's ANDA products, in accordance with

1 you have a table in Section 2.7 that's setting forth a four- to  
2 nine-month timeframe window, correct?

3 A. Yes, four to nine months is included in this table.

4 Q. Would that be infringing?

5 A. No, this section does not infringe the claims.

6 Q. So if a patient came to you, Dr. Berger, after being on  
7 PP3M or you put that patient on PP3M and comes back within four  
8 to nine months, is switching to a tablet an option that you  
9 would consider clinically?

10 A. Yes, certainly one of the many options.

11 Q. Going back then to Dr. Sommi, who you are rebutting here,  
12 you've just outlined sections in the label that are  
13 non-infringing.

14 Did Dr. Sommi provide any analysis regarding  
15 non-infringing uses in his opinions at all?

16 A. I saw none in his testimony or in his report.

17 Q. All right. Thank you for that, Dr. Berger.

18 I want to go to your point about no encouragement or  
19 control.

20 Let's go -- now, earlier you testified that  
21 prescribers have no control over whether their patients return,  
22 nor do they know when the patient will return for treatment; is  
23 that correct?

24 A. Yes.

25 Q. Do you recall that testimony?

1 In your 50 years of experience -- and granted, Trinza  
2 has been around since 2015 -- do you ever recall having a  
3 patient who had schizophrenia, misses his or her dose of PP3M,  
4 returns between a four- to nine-month window, not one day  
5 before, not one day less, and you treated them exactly in  
6 accordance to the table that we just saw in that linear  
7 fashion? Do you ever recall doing that?

8 A. I recall that I have never done that.

9 Q. Okay. Just for argument's sake, again, knowing that you  
10 have never encountered that, if that were to occur, in your  
11 opinion, would that be exceptional?

12 A. If I were to follow the table?

13 Q. No. Just having that situation itself, the patient  
14 missing a dose of PP3M, coming back within four to nine months  
15 and then following that particular regimen, if that were to  
16 occur, would that be exceptional?

17 A. Yes, it certainly would be exceptional. Uncommon.

18 Q. Dr. Berger, Dr. Sommi has testified -- and you might even  
19 get this on cross -- that it's inevitable that a prescriber  
20 would infringe that one lone section of -- one lone portion of  
21 Section 2.3 in the entirety of the prescribing information.

22 Do you agree with that opinion, that it is inevitable  
23 that someone would infringe?

24 A. No, I don't agree with that.

25 Q. Why not?

1 Trinza label says about dosing a patient who last received a  
2 dose of Trinza between four and nine months ago, right?

3 A. I am familiar with what it says, yes.

4 Q. Dr. Berger, the instructions on the Invega Trinza label  
5 for dosing a patient who last received Trinza four to nine  
6 months ago are the same as the dosing regimen in Claim 5 of the  
7 '693 patent, right?

8 A. It's not an instruction.

9 Q. But my question is, is the Invega Trinza label the same as  
10 Claim 5 of the '693 patent?

11 A. That wasn't your question.

12 Q. Well, my question now is, is the Invega Trinza label the  
13 same as Claim 5 of the '693 patent?

14 A. The table is the same as in the prescribing information.

15 Q. Well, when I asked you at your deposition, you said yes,  
16 right?

17 A. I don't know. You'll have to show me my deposition.

18 Q. Let's go to page 150 of the transcript.

19 MR. MUKERJEE: Your Honor, I'm sorry, how is this  
20 impeachment? The witness just testified --

21 MR. FISCHER: Well, I just asked him what he said and  
22 he said "You'll have to show me."

23 MR. MUKERJEE: But that's right. It's not right,  
24 Aron. This isn't proper impeachment.

25 MR. FISCHER: He gave a different answer from what he

1 gave in his deposition.

2 THE COURT: I'll allow it.

3 BY MR. FISCHER:

4 Q. Dr. Berger, this is at line 12 of page 150.

5 "Question: And the Invega Trinza label is the same  
6 as Claim 5 of the '693 patent, right?

7 "Answer: That's my understanding, yes."

8 Did I ask you that question and did you give that  
9 answer, Dr. Berger?

10 A. When you asked me this question, you were referring to the  
11 table and my answer was in regard to that. When I said that's  
12 my understanding, that was my understanding of what you were  
13 asking.

14 Q. Okay.

15 The question was did I ask you that question and did  
16 you give that answer?

17 A. The text speaks for itself. I'm explaining why it says  
18 that.

19 Q. Thank you, but if you could, just answer the question,  
20 too, please.

21 The question is did I ask you that question and did  
22 you give that answer?

23 A. The text speaks for itself. Yes, that's what it says.

24 Q. You also reviewed a label for Mylan's proposed ANDA  
25 product; is that right?

1           Isn't it true, Dr. Berger, that in your experience, a  
2     large percentage of patients who are on Invega Trinza miss  
3     doses?

4     A.     Yes.

5     Q.     And you've estimated that more than 50% of the patients on  
6     Trinza that you've treated are noncompliant, correct?

7     A.     I did say that, yes.

8     Q.     Okay. And of the patients that miss doses, you  
9     estimated -- you've estimated that about 20 to 30% of them come  
10    back for another appointment 16 or more weeks later, right?

11    A.     I don't remember the numbers, but, yes, I probably said  
12    that.

13    Q.     And is that correct?

14    A.     Yes, I think that is correct.

15    Q.     Okay. Now, Dr. Berger, a couple weeks back, when we were  
16    delivering opening statements on infringement -- I'd like to go  
17    to the next slide.

18           My colleague, Ms. Mullin, referred to your deposition  
19    testimony where you said that more than -- that it would be  
20    fair to say that more than 50% of the patients on Trinza that  
21    I've treated are noncompliant.

22           And then in their opening statement, Mylan's counsel  
23    said that this was misleading. They said --

24           MR. MUKERJEE: Your Honor, Dr. Berger wasn't there  
25    and he hasn't laid any foundation whether he's reviewed the



1 testified that he didn't recall whether he was asked. So  
2 that's what impeachment is.

3 MR. MUKERJEE: It's not.

4 THE WITNESS: Is there a question?

5 BY MR. FISCHER:

6 Q. Yes. Did I ask you that question and did you give that  
7 answer?

8 A. I have to explain my answer.

9 Q. Can you answer the question first, please?

10 A. I'm under oath to tell the truth.

11 Q. It's a yes-or-no question.

12 A. The text says what it says. The text says that. I agree  
13 that the text says that.

14 Q. So now I'll ask a question, a different question, which is  
15 isn't it true that you have supervised residents who  
16 reinitiated patients on Trinza who have last seen Trinza at  
17 least four months ago and fewer than nine months ago?

18 A. It is true that I have supervised residents who have tried  
19 to reinitiate patients, yes. I'm not saying that they were  
20 successful and they went through all the steps.

21 Q. The residents that you have supervised who re-initiate  
22 patients according to the Trinza label specifically, that was  
23 for patients who last received Trinza between four and nine  
24 months ago, correct?

25 A. Yeah, they tried but they were unsuccessful.

1 Q. And you didn't come -- there have been times when they  
2 re-initiated patients on Trinza, right?

3 A. Well, for instance, they re-initiated the first  
4 re-initiation loading dose, but not the second.

5 Q. Did they re-initiate patients on Trinza according to the  
6 label?

7 A. According to the label, they tried but they were  
8 unsuccessful.

9 Q. Okay. And you testified differently at your deposition,  
10 didn't you?

11 A. Well, you didn't let me finish in the deposition.

12 Q. Did I interrupt you in your deposition?

13 A. I don't remember, but the text says that we didn't get to  
14 that part.

15 MR. FISCHER: I apologize. I have to impeach again  
16 because he's giving a different answer.

17 BY MR. FISCHER:

18 Q. Didn't I ask you the question "Have you supervised  
19 residents who re-initiated patients on Trinza according to the  
20 instructions on the Trinza label after a patient had last  
21 received Trinza at least four months ago and fewer than nine  
22 months ago?" and didn't you answer "There have been times,  
23 yes"?

24 A. I'm clarifying for you what re-initiating means in this  
25 particular sentence.

1 Q. You're testifying differently than you testified at your  
2 deposition, right?

3 A. I'm clarifying it.

4 Q. All right.

5 So let's take a look at what Mylan's label  
6 instructions say about missed doses. This is --

7 MR. FISCHER: I guess now we'll have to close the  
8 Court?

9 MR. MUKERJEE: Right. Thank you. Thanks.

10 So, Your Honor, in keeping with --

11 THE COURT: Okay, gentlemen.

12 Sir, step out.

13 And if there's anyone else who is not related to  
14 either of the represented parties or court --

15 Court personnel may remain.

16 MR. MUKERJEE: Your Honor, thank you again.

17 THE COURT: You're welcome.

18 MR. FISCHER: May I proceed?

19 THE COURT: Yes, please.

20 BY MR. FISCHER:

21 Q. So this is PTX-162. It's in your binder. We'll put it on  
22 the screen as well. This is Mylan's proposed label for PP3M.

23 On the first page, at the bottom left, it refers to  
24 missed doses, right?

25 A. Yes.

1 A. That's what it says.

2 Q. So the label's making a conditional statement here, right?

3 A. If -- yes. "If" is a conditional statement.

4 Q. So it's saying don't miss doses, but if you do miss doses,  
5 go to table two, right?

6 A. That's what it says.

7 Q. And then table two, as we've discussed, is the same  
8 re-initiation regimen as found in Claim 5 of the '693 patent,  
9 correct?

10 A. It's a description of the doses and the timing of the  
11 re-initiation regimen, yes.

12 Q. That's the same as the patent?

13 A. Yes.

14 Q. Now, Dr. Berger -- and I think you mentioned this again on  
15 direct -- you said that in your practice -- it may have been  
16 the last question you were asked on direct, actually -- you  
17 said you don't follow the recommendations in table two for  
18 patients who come back four to nine months after their last  
19 dose, right?

20 A. I testified that it has not happened in my recollection in  
21 my practice.

22 Q. Though it has happened with the residents under your  
23 supervision, right?

24 A. No, it has not.

25 Q. Okay. Despite what you said at your deposition?

1 A. I clarified -- I tried to clarify.

2 Q. Okay.

3 A. But you wouldn't let me.

4 Q. So, for patients who come back between four and nine  
5 months since their last dose of Trinza, your recommendation is  
6 just to give them another dose of PP3M, right?

7 A. Well, that has been my practice and my recommendation,  
8 yes.

9 Q. And that's because you think it's undesirable to ask a  
10 patient who's already shown themselves to be noncompliant by  
11 missing a dose to come back for multiple re-initiation doses of  
12 PP1M, right?

13 A. I have to explain. Not undesirable. It's unsafe and it's  
14 unreasonable because these are noncompliant patients and they  
15 don't do that. So the dose regimen cannot be followed when the  
16 patient doesn't show up, even if it's a re-initiation dosage  
17 schedule. If the patient doesn't show up, it can't be done.  
18 That's what I'm saying that this patent calls for. It calls  
19 for something that can't be done.

20 Q. So it's your view, if I understand you correctly, that the  
21 instructions in Claim 5 of '693 patent are unreasonable and  
22 unsafe.

23 Is that right?

24 A. That's my testimony, yes.

25 Q. So before Invega Trinza came out, if someone had showed

1 you the missed dose instructions of Claim 5 and said, is this a  
2 good idea for how to dose a patient who had their last dose  
3 four to nine months ago, you would have said it was a bad idea,  
4 right?

5 A. Yes.

6 Q. You would have said it was unreasonable, right?

7 A. Yes.

8 Q. You would have said it was unsafe?

9 A. Yes.

10 Q. You would have said don't do it, right?

11 A. I would have said be guided by the standard of care, not  
12 by the package insert.

13 Q. This is with no package insert.

14 A. What's the question?

15 Q. I'll withdraw the question.

16 Dr. Berger, some health care providers do follow  
17 label instructions for patients who have missed a dose of PP3M  
18 by four to nine months, right?

19 A. I'm sure they try.

20 Q. And you're sure they do, right?

21 A. No.

22 Q. Well, when you say they try, they administer the doses  
23 called for by the -- by Claim 5, correct?

24 A. I'm sure there are instances in which they try, but if the  
25 patient doesn't show up, the regimen cannot be implemented.

1 Q. Sometimes the patient will show up, right?

2 A. Sometimes patients show up, yes.

3 Q. And sometimes the patient will be in a facility where they  
4 don't have to show up because they're already there, right?

5 A. That sometimes happens, yes. But even in that case, the  
6 patient may still refuse it.

7 Q. And patient has to agree to get the injection, right?

8 A. Yes.

9 Q. That's true of almost all drugs, right?

10 A. Yes. Only in emergencies can a medication be given  
11 without a patient's consent.

12 Q. Now, at your deposition, you compared the label  
13 instructions to the speed limit.

14 Do you remember that?

15 A. Yes.

16 Q. So, the label instructions are the speed limit telling you  
17 what the government wants you to -- how fast the government  
18 wants you to drive, right?

19 A. Now, you'll remember that in my deposition, I said no,  
20 those are not instructions, there are no instructions here.

21 Q. Well, they're like the speed limit, right?

22 A. It's not an instruction.

23 Q. Is it like the speed limit?

24 A. Yeah, it's like the speed limit. It's guidance. This is  
25 what somebody thinks is a good idea.

1 here was in the present tense?

2 A. I'm saying that the claim is in the present tense. The  
3 claim talks about what happens. Obviously if we're talking  
4 about one point in time, there's some things that happened in  
5 the past, some things that happened in the future, but this  
6 claim talks about a patient missing a dose. That's part of  
7 this claim. That's exactly what this claim is about. Even the  
8 file history says that.

9 Q. Okay. The language of the claim says it happened four to  
10 nine months ago, right?

11 A. The claim says, "Wherein said patient had last been  
12 administered a PP3M injection four to nine months ago." That's  
13 what the claim says.

14 Q. Okay.

15 And then what the claim says is that there are three  
16 steps for administering a paliperidone palmitate injection to  
17 such a patient, right?

18 That's what the claim says?

19 A. The claim lists three steps in writing; however, as I  
20 testified, there are seven steps to this claim.

21 Q. Just focusing for now on what the claim says.

22 A. Okay.

23 Q. It says that step one is administering intramuscularly in  
24 the deltoid muscle of said patient a first re-initiation  
25 loading dose of PP1.



1 Q. But -- I'll move on.

2 Isn't it true patients for any treatment that's  
3 administered by a health care professional at a health care  
4 facility have to show up?

5 A. Under ordinary circumstances, yes.

6 Q. That's your opinion about Trinza, right? That they have  
7 to show up for their doses?

8 A. Of course.

9 Q. And then it's also true of any other injectable that's  
10 administered by health care professionals, right?

11 A. Under ordinary circumstances, yes.

12 Q. Dr. Berger, you're familiar with medications that are  
13 indicated for treating patients who have been overdosed, right?

14 A. Yes.

15 Q. And you would consider the patient overdosing to be the  
16 first step in a dosing regimen for a drug indicated to treat  
17 overdose, right?

18 A. If the package insert says the patient has to overdose and  
19 then come in for treatment, yes, I would consider that.

20 Q. And then assuming that the patient voluntarily overdosed,  
21 then it would be the patient who carried out that step of the  
22 dosing regimen, right?

23 A. Yes. If the patient was doing what the package insert  
24 told him to do, then yes.

25 Q. I want to go back briefly to your seven-step theory. I

1 want to go back to your demonstrative. Actually, we'll go  
2 here, to Claim 5 with the seven steps.

3 Now, there's a couple of steps missing here, aren't  
4 there, Dr. Berger?

5 A. You'll have to tell me what you mean.

6 Q. Well, in your opinion, isn't the first step of Claim 5 to  
7 evaluate the patient?

8 A. Specifically talking about Claim 5, no. The first step is  
9 the patient misses the dose.

10 Q. Then the next step is to evaluate the patient, right?

11 A. The next step is the patient has to show up four to nine  
12 months later so that the health care professional can evaluate  
13 the patient.

14 Q. There's a step here for evaluating a patient that's  
15 missing from your seven-step theory, right?

16 A. I don't understand.

17 Q. Well, you testified at your deposition that one of the  
18 steps of Claim 5 was to evaluate the patient, right?

19 A. Steps three, five and seven include the health care  
20 professional evaluating the patient and determining the  
21 indicated treatment. And if the patient agrees, then treating  
22 the patient.

23 Q. So let's look at your deposition at 130, 19. It's  
24 actually the passage we looked at a minute ago.

25 I asked you, "You'd agree that Claim 5 states that

1 the first step of the dosing regimen is administering  
2 intramuscularly in the deltoid muscle of said patient a first  
3 re-initiation loading dose of PP1M?"

4 You said, "I agree it says that, but that's not  
5 correct."

6 Then I said, "Okay. So why is that not correct?"

7 You said, "The first step is to evaluate the  
8 patient."

9 Do you recall that?

10 A. That was referring to step number three. What I'm now  
11 calling step number three, what you're calling step number one.

12 Q. Then there's another step where the patient has to  
13 cooperate and consent, right?

14 A. Well, that's part of the process. It isn't listed as a  
15 step, but it's part of the process.

16 Q. It's part of the process for all methods of treatment,  
17 right, for the patient to cooperate and consent?

18 A. Yes.

19 Q. There's a lot of other things that have to happen for this  
20 dosing regimen of Claim 5 to be given, right?

21 A. A lot of steps have to happen in the process of any  
22 medical procedure, yes.

23 Q. That's your opinion here, is that there are a lot of steps  
24 that have to occur.

25 In order for this dosing regimen to be given, a lot

1 unsuccessful in implementing that regimen?

2 A. So if the resident presents to the patient as  
3 re-initiation regimen and recommends it, the patient agrees,  
4 they start it out, the patient has to return for the second  
5 re-initiation loading dose, and then the patient has to return  
6 for the re-initiation PP3M dose, and if the patient doesn't do  
7 that, Claim 5 doesn't apply because it wasn't completed.  
8 That's what I was referring to.

9 Q. Okay. And I think you also said that about 20 to 30% of  
10 Trinza patients return more than 16 weeks, right? And that  
11 that would include patients -- well, let me ask you this:

12 Do you recall that? Do you recall on cross actually  
13 saying that 20 or 30% of Trinza patients returned more than 16  
14 weeks after their PP3M injection?

15 A. Yes.

16 Q. So that time period you talked about, more than 16 weeks,  
17 would that -- could that include more than nine months then?

18 A. Yes.

19 Q. Okay. And the claim, though, wouldn't cover that, right?  
20 It wouldn't cover more than nine months, would it?

21 A. Correct.

22 MR. MUKERJEE: Okay. Now, counsel asked you  
23 questions on, I believe, PTX-0135 to 0046. Okay. And that is  
24 in your binder. But maybe we could just pull up PTX-135. And  
25 I'm -- specifically, Scott, I'm going to 0046.

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

CIVIL ACTION NUMBER:

Plaintiffs,  
vs.

2:20-cv-13013-EP-LHG

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

BENCH TRIAL VOL. 3

Defendants.

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
December 1, 2022  
Commencing at 10:03 a.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
UNITED STATES DISTRICT JUDGE**

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412

1 non-prodrug oral form. So a lot was known about it and a lot  
2 was known about how you could control depot injections and  
3 affect their absorption rate. So much was known about  
4 paliperidone palmitate's basic pharmacokinetics, about the  
5 effects of particle size, and then target exposure efficacy, so  
6 the therapeutic window, the blood concentrations that you want  
7 shoot for at steady state to effectively treat patients, that  
8 was well understood from various art on the PP1M formulation,  
9 such as the '519, the '536, and the Sustenna label that I'll  
10 talk about more further later.

11           It was known that the PP1M could be used to treat  
12 schizophrenia. It was known that you needed missed -- or that  
13 missed dose regimens were useful. It was known that those  
14 could be useful, and it was useful to have alternative  
15 regimens, depending on how long it had been since a patient  
16 last had a dose. You know, how long they missed had their dose  
17 by.

18           And then it was known that if patients fell in an  
19 intermediate or middle window where, you know, they didn't have  
20 so much drug in their body that you could just put them right  
21 back on their maintenance doses and ignore the fact that they  
22 had missed part of a dose, you had this window where you need  
23 to do something to reinitiate them, but they still had some  
24 drug in their body, so you didn't want to treat them like  
25 they're naive. You didn't need to put them through a whole

United States District Court  
District of New Jersey

**Appx02383**

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425

1 The present application provides a method for treating patients  
2 in need of psychiatric treatment, wherein said patient misses a  
3 stabilized dose of a monthly maintenance regimen of  
4 paliperidone palmitate.

5 Q. Who is the applicant of the '536 publication?

6 A. Janssen.

7 Q. And so like the '519 publication, did Janssen provide  
8 windows with respect to a patient missing a dose of a monthly  
9 paliperidone palmitate formulation?

10 A. Yes, they do.

11 Q. And before we jump into each one, at a high level, do you  
12 recall what those windows are?

13 A. Yes, there were three windows in it. Essentially, the  
14 same windows, although they expanded the limits a little bit,  
15 but a first window, a second window and a third window. And  
16 then it provides reinitiation regimens for those. And the  
17 first window was up to six weeks since they missed a dose, so  
18 four to six weeks since their last dose. And I think we'll  
19 discuss the others in more detail, or I have the slides for the  
20 others in more detail.

21 MR. SODERSTROM: Yeah, let's actually pull up the  
22 exhibit, Scott, if we could. Maybe go to DTX-97.0011. And if  
23 we highlight Paragraph 42. It's in the right column there.

24 BY MR. SODERSTROM:

25 Q. Dr. Forrest, is this the first window that you were just

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District of New Jersey

**Appx02396**

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426

1 referring to?

2 A. Yes, a method for reinitiation providing for patients that  
3 missed a dose more than four weeks and less than six weeks ago  
4 where you administer a deltoid first loading, a second -- or  
5 you administer a first deltoid and then continue administering  
6 deltoid or gluteal muscle maintenance doses on about the 23rd  
7 to 37th day. So, essentially, to break it down, they're just  
8 saying continue your maintenance dosing as soon as possible is  
9 what this distills down to.

10 MR. SODERSTROM: Scott, can you blow up paragraph 43?

11 BY MR. SODERSTROM:

12 Q. Dr. Forrest, can you explain what Janssen discussed at  
13 paragraph 43 of its '536 publication?

14 A. Yes, it's a bit longer here, so I'll partially summarize  
15 here. But wherein more than six weeks but less than six months  
16 have elapsed since the patient received a last dosing of  
17 paliperidone palmitate, the reinitiation regimen may comprise a  
18 first loading dose, a second loading dose, and a maintenance  
19 dose.

20 And that first loading dose should be administered as  
21 soon as possible, about a week later, into the deltoid. And  
22 then there should be a second loading dose about a week after  
23 that. And then you should resume the monthly maintenance  
24 dosing a month later. And then -- and I'm briefly paraphrasing  
25 because I believe I have some slides in more detail here, but

United States District Court  
District of New Jersey

**Appx02397**



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427

1 those first two loading doses, their strength depends on their  
2 previously stabilized dose that they were stabilized on before  
3 they missed, except for the high strength, in which case you  
4 would use one strength below that to reinitiate them with  
5 before you put them on maintenance dosing.

6 Q. And I just want to pause briefly because you spoke about  
7 loading doses and using those to get into your steady state for  
8 an initiation dosing regimen. Here, it's talking about loading  
9 doses again, but with respect to a reinitiation regimen. Can  
10 you just explain what the purpose of the loading dose is here  
11 with respect to a reinitiation dosing regimen?

12 A. Well, it doesn't matter if you're completely naive and you  
13 have no drug in your body or if you just have a shortage of  
14 drug in your body because you've missed a dose for a while.  
15 For you to achieve steady state rapidly with your normal  
16 maintenance dosing, you've got to replace that drug that should  
17 be there, you know, that foundation that you should have from  
18 previous dosings. You know, even if you're naive, for example,  
19 where you have none.

20 So the purpose of the loading dose is just get your  
21 plasma levels up rapidly to get you into that steady state  
22 range quickly so that the normal maintenance doses can maintain  
23 you in the steady state range.

24 Q. If we go to paragraph 45, and it might split across the  
25 bottom of DTX-9711 and on to DTX-9712.

United States District Court  
District of New Jersey

**Appx02398**

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428

1 Dr. Forrest, can you explain what's being disclosed  
2 by Janssen at paragraph 45 of their '536 publication?

3 A. So when more than six months have elapsed since the  
4 patient received the last dosing of paliperidone palmitate, the  
5 reinitiation regimen may comprise a first loading dose, a  
6 second loading dose, and a maintenance dose. The first loading  
7 dose may be administered as soon as possible, the second dose  
8 about the eighth day, but then they say down later that that  
9 can be about the seventh day plus or minus two days, so about a  
10 week later. And the maintenance dosing may be administered on  
11 about the 30th day after the first loading dose. But again,  
12 down below that, they say that's plus or minus seven days. So  
13 about a month after the second loading dose.

14 Essentially, this is -- because of the dosings, this  
15 is essentially the naive initiation procedure they're using  
16 here.

17 Q. And so do I have it right that in both Janssen's '519  
18 publication and Janssen's '536 publication, there were three  
19 windows to consider when a patient misses a dose?

20 A. Yes, you do.

21 Q. Separate from these windows of a patient missing a dose --

22 MR. SODERSTROM: And perhaps we go back to the slides  
23 here, Scott, slide 29.

24 BY MR. SODERSTROM:

25 Q. Do you know what an administration interval is?

United States District Court  
District of New Jersey

**Appx02399**

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443

1 you would understand it. For those two doses, the first one as  
2 soon as possible and the second one in the deltoid one week  
3 later, are those equivalent to what you were describing earlier  
4 as reinitiation loading dosages?

5 A. Yes, it is.

6 Q. Now, if we move to the next slide, did you create a slide  
7 showing how the timing of the patient missing a maintenance  
8 dose impacts the dosing for the three different pieces of prior  
9 art from Janssen that we've discussed at this point?

10 A. Yes, I did.

11 Q. Can you just walk us through that slide?

12 A. So, all three of them give essentially the same, though  
13 there's slight differences in numbers, but they all give  
14 essentially the same three windows and regimens. So the first  
15 window of four to six weeks since the last injection, just  
16 resume. Go back to whatever dose was previously administered  
17 and resume monthly injections.

18 Then there's a second window of six weeks to six  
19 months since the last injection, and you have a modified or  
20 reinitiation loading dose regimen here. You give a deltoid  
21 immediately, a second deltoid a week later, and then deltoid or  
22 gluteal shots a month after that of their normal, stabilized  
23 monthly dosage regimen. The strength of medication you use for  
24 those two first two injections or loading injections or  
25 reinitiation loading injections depends on what their

United States District Court  
District of New Jersey

**Appx02414**

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444

1 stabilized missed dose was.

2 Then there's a third window where it's been six or  
3 more months since their last injection and you restart the  
4 patient. You treat them as if they were essentially naive.

5 Q. So these three pieces of prior art that we've discussed at  
6 this point were focused on a PP1M formulation or formulations;  
7 is that fair?

8 A. Yes.

9 Q. Was there any prior art at all discussing dosing regimens  
10 for PP3M?

11 A. There was prior art on dosing regimens for PP3M but not on  
12 the reinitiation.

13 Q. Let's go to the next slide, which shows portions of  
14 DTX-026. Are you familiar with what DTX-026 is, Dr. Forrest?

15 A. Yes, it's what I refer to as the JAMA study.

16 Q. What does JAMA discuss, at a high level?

17 A. Well, JAMA was a -- what they call a double blind placebo  
18 controlled study of relapse in patients that was to evaluate  
19 the efficacy and the safety of a three-month formulation of  
20 paliperidone palmitate versus placebo in treating patients that  
21 had been previously dosed or stabilized on a once-monthly  
22 paliperidone palmitate.

23 Q. And what did JAMA say regarding the effectiveness and  
24 safety of the PP3M formulation that was part of the study?

25 A. They found that the PP3M was both safe and effective.

United States District Court  
District of New Jersey

**Appx02415**

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445

1 Q. Let's go to the next slide.

2 Actually, before we do that, can you explain to me in  
3 the bottom right, we discussed this a bit during yesterday's  
4 opening, but can you explain what this eTable One dosing  
5 administration schedule from DTX-26.0067 shows?

6 A. Well, it shows that you should first initiate a patient on  
7 PP1M before giving them maintenance doses of a PP3M, and it  
8 provides a dosing regimen for doing this with a PP1M product,  
9 which is the loading steps, and then they do stabilize on this  
10 one just because they're also finding what is an effective dose  
11 in the patient. Then, they then continue with PP3M doses, and  
12 the PP3M dose is based upon their PP1M dose.

13 Q. If we go to the next slide, this is a table that we're  
14 becoming more and more familiar with as well, eTable Two,  
15 conversion between PP1M and PP3M doses from DTX- 26.0068.

16 What does that show?

17 A. Well, so this shows how to convert between a PP1M and a  
18 PP3M dosage form. So, while it's not threefold exact  
19 difference between them, they show that you use a dose of PP3M  
20 that is 3.5 fold your dose of PP1M. Meaning, the PP1M dose  
21 would be one divided by 3.5 of the PP3M dose. So it provides a  
22 conversion factor table here between PP3M and PP1M doses, and  
23 it does this both in terms of milligrams of paliperidone  
24 palmitate and in terms of milligram equivalents of  
25 paliperidone.

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449

1 A. Yes.

2 Q. Do you recall also looking at the patent office's  
3 rejection earlier today over the '906 patent which was directed  
4 to an initiation regimen for PP1M?

5 A. Yes.

6 Q. JAMA did disclose as we just looked --

7 MR. SODERSTROM: And Scott, if you could, go back to  
8 slide 32.

9 BY MR. SODERSTROM:

10 Q. JAMA did disclose an initiation regimen to get onto PP3M,  
11 right?

12 A. Yes, it did.

13 MR. SODERSTROM: I have a few -- two, three,  
14 relatively short references, Your Honor, that I was thinking  
15 maybe we would go to and it would be a good stopping point, if  
16 that works for you and Dr. Forrest?

17 THE COURT: That's fine.

18 MR. SODERSTROM: Let's move to slide 34 and another  
19 publication.

20 BY MR. SODERSTROM:

21 Q. This next slide shows an excerpt from DTX-021.

22 Dr. Forrest, do you know what this document is?

23 A. Yes, this is what I called the NCT-423. So when a company  
24 or even a hospital, a sponsor -- or a sponsor sponsors a  
25 clinical study, they register it with clinicaltrials.gov to

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District of New Jersey

**Appx02420**

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462

1 Q. So it's the same for both the timing of the injection and  
2 the location of the injection?

3 A. Yes.

4 Q. Now, I want to go back to our discussion that we had a  
5 little bit earlier before lunch about half-lives.

6 Based on the prior art, how long would a POSA expect  
7 a half-life of PP3M to be?

8 A. Well, they would expect, and based on, you know, the prior  
9 art, that the half-lives were -- there are one to two  
10 half-lives of administration intervals. So they would expect  
11 it to be about the same as the length of time the depot lasts  
12 between injection. So for a PP3M, they would expect it to be  
13 about 90 days, like it was about a month for the PP1M.

14 Q. So if a POSA were to consider missed dose information for  
15 a PP3M formulation, how does that half-life impact what the  
16 timing aspect of that window might be?

17 A. Well, you would look at the windows and understand that  
18 there'd be a similar relationship subject to some routine  
19 optimization, but similar relationship in when those windows  
20 would begin and end, as there was for the earlier PP1M dosage  
21 form.

22 Q. So based on half-lives and administration intervals that  
23 you just referenced -- let's start with the front end -- how  
24 would a POSA use those in determining the starting point of a  
25 middle window with respect to devising a PP3M regimen?

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463

1 A. Well, they'd understand that the goal is to get a patient  
2 back so that the regular maintenance dosing will get them  
3 within the equilibrium range really quickly. And we knew from  
4 the older dosage form if the patient missed a dose by about a  
5 half of a half-life -- which in this case was two weeks, six  
6 weeks since the last injection -- they're getting to the point  
7 where you need to think about a loading dose because they lost  
8 enough drug from their body that you can't just jump back in  
9 and resume.

10 The whole idea is you want to give the maintenance  
11 dose and they'll be within the therapeutic steady state window.  
12 You don't want them to have to take time to get back to the  
13 steady state quickly because it's bad not to be steady state.  
14 You want to be steady state. So you take a similar approach.  
15 It's around one-half, 1.4, something like that. So similar --  
16 so about a multiplier of that. And you'd end up with about 126  
17 days, actually, which is just over four months.

18 Well, yeah, for half-life, it's about 4.2 months,  
19 four and a half months, in that range.

20 Q. If a POSA were looking to determine the end of a middle  
21 window for a potential PP3M formulation, how would they go  
22 about doing that using half-lives?

23 A. They would know that a patient would be essentially naive.  
24 They wouldn't have any drug left in their body after about four  
25 or five half-lives. So that's an important consideration.

United States District Court  
District of New Jersey

**Appx02434**



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464

1 And they also look at the -- you know, the past  
2 formulation of PP1M, where it was six months. So five  
3 half-lives after their missed dose. And they look again and  
4 they'd see -- you know, this is when you feel they're  
5 essentially naive, that they've essentially got all the drug  
6 out of their body by 18 months. You also think about the other  
7 prior art, if that's too long or not. So you'd also look at  
8 other art, too.

9 You'd be concerned -- especially in the back end --  
10 there's such a risk that the person may not get up to steady  
11 state quickly. You don't want to risk that. So you would look  
12 at prior art, too, in addition to what you knew about the  
13 half-lives.

14 Q. For example, what did the prior art '536 publication teach  
15 regarding administration intervals and half-lives?

16 A. Well, it taught the administration intervals were similar  
17 to half-lives, so they're about equal.

18 Q. Did they say anything as to when one might expect a drug  
19 to be eliminated from the body based on the number of  
20 half-lives?

21 A. They taught that after four to five half-lives, that  
22 essentially all the drug had been eliminated from the patient's  
23 body.

24 Q. So with that information, how would a POSA go about  
25 devising when the end window might be for a middle window after

United States District Court  
District of New Jersey

**Appx02435**

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465

1 a patient misses a dose?

2 A. Well, they would look at those data and they would say  
3 that, well, I know here by four or five half-lives, so  
4 somewhere between 12 and 18 months in there that people are  
5 essentially naive and they have no drug left in their body at  
6 that point.

7 Q. Was there other prior art that you also considered?

8 A. Well, as I said, there was a lot known about PP3M already  
9 and the real danger is a patient relapsing. You want to  
10 prevent that. You also look at a lot of other prior art that  
11 was known about a PP3M to see if your estimates made sense or  
12 not, that you initially made. You don't want a patient to  
13 relapse.

14 Q. If we go to the next slide, one of the criticisms from  
15 Plaintiff's expert is that in his opinion -- I'll quote it --  
16 "JAMA's discussion of the clinical results states, 'Patients at  
17 risk from sudden discontinuation from treatment could,  
18 therefore, benefit from three-month paliperidone palmitate  
19 providing protection from relapse for up to one year after the  
20 last dose.'" And teaches away, in his opinion, from utilizing  
21 the claimed missed dose reinitiation dosing regimen for the  
22 four to nine months patient population specified in Claim 5.

23 Do you agree with that, Dr. Forrest?

24 A. No, I don't. You would actually not just look at that  
25 statement, but you would also look at the graph that they were

United States District Court  
District of New Jersey

**Appx02436**

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466

1 basing part of this off of. This is figure two from the DTX-26  
2 here.

3 What figure two is, it's actually a plot of what  
4 portion of patients had relapsed when they put them on the  
5 placebo part of this study of the paliperidone palmitate.

6 To understand the way this worked, the patients got a  
7 dose of PP3M, and then when they were supposed to come back in  
8 three months later, they either got placebo, so it was just a  
9 lipid injection with no drug in it, or they got the PP3M.  
10 They're looking to see how long before patients relapse. So  
11 really, it was simulating a missed dose and times of missed  
12 dosing.

13 You look at this and one thing I'd caution, just  
14 because it's a little difficult to read, but you see there's  
15 days down here at the bottom? So that's days since they missed  
16 injection. I mean, since they missed a maintenance dose.

17 We've been really talking today about time since they  
18 had their last dose. So what you actually have to do is add 90  
19 days to all these numbers down at the bottom to really  
20 understand it.

21 So if we look here and we see protection from relapse  
22 for up to one year, that would be about 274 days on this graph.  
23 So a year minus three months approximately.

24 And you see there that actually just over 50% of  
25 patients have actually relapsed at that point. There's this

United States District Court  
District of New Jersey

**Appx02437**

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467

1 yellow band around that that goes up and down, and this is  
2 called a confidence interval. So one issue with any clinical  
3 study is you're trying to understand how the whole world will  
4 respond, all potential patients, but you can't measure all  
5 potential patients.

6 So you do a study, you have a limited number, and you  
7 build what is called a confidence interval. So you feel that  
8 the true average is somewhere in between that band there. And  
9 if you look at this one, you see that that band may be all the  
10 way down from 20 to 70%, so as much as 80% of patients might  
11 have fell already by a year. And even if you look at their  
12 actual data down here, you see that a huge number of patients  
13 had dropped out of the study by a year due to failure or other  
14 reasons. We knew they were -- you don't know all the full  
15 reasons, but a large number dropped out. So there's less than  
16 10% of the starting patients even left at that point, and then  
17 you know that a great deal of them will relapse.

18 So a POSA doesn't want to risk -- we know they're  
19 definitely now I mean, possibly as many as 80% of patients are  
20 naive at this point by 12 months. Remember, the goal is to get  
21 them back to equilibrium, steady state as quickly as possible.  
22 You need to consider when do I need to switch from this  
23 modified lower reinitiation regimen to just treating them as if  
24 they're completely naive.

25 The natural jump there is -- well, let's look at an

United States District Court  
District of New Jersey

**Appx02438**

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468

1 administration interval before this. We can jump back on here  
2 to 180 days, which is actually nine months, and we see now here  
3 that somewhere around 70%, perhaps -- it's a little hard to  
4 draw over to the line around here. But maybe 60 to 70% of  
5 patients are still being effectively treated, but you're just  
6 touching on that edge where there's -- the study has some  
7 variability. We know it could be the median. There's a 5%  
8 chance the median could be at 50% right there already at nine  
9 months.

10 This is a natural point where you know most  
11 patients -- you know, over half the patients are still being  
12 treated. They still obviously have some drug in their body.  
13 You look at this as a point -- around nine months is what I  
14 would see from JAMA, if I'm thinking in terms of administration  
15 intervals, is when I need to start thinking about treating  
16 patients. Beyond this, I need to start thinking about treating  
17 them as naive, because definitely after nine months, most of  
18 them have failed, possibly as many as 80%.

19 Q. Based on your review of the prior art we just discussed,  
20 including JAMA, a POSA would put an endpoint to a middle window  
21 of a three-month formulation at what time?

22 A. Nine months.

23 MR. SODERSTROM: Scott, can we pull up Plaintiff's  
24 opening slide 31 from yesterday?

25 BY MR. SODERSTROM:

United States District Court  
District of New Jersey

**Appx02439**

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477

1 for treating schizophrenia from the Sustenna label.

2 Q. Let's go to the next slide, Claim 10 of the '693 patent.

3 What does that claim cover?

4 A. This is a method claim wherein the second reinitiation  
5 dose of PP1M is administered seven days after the first  
6 reinitiation dose of PP1M.

7 Q. Is it your opinion that that claim is obvious?

8 A. Yes, it is. The seven days or about a week was taught  
9 also in the prior art we discussed between the two initiation  
10 doses.

11 Q. Just for clarification, which prior art are you referring  
12 to?

13 A. I said initiation. I meant reinitiation. This was the  
14 '519, the '536, the Sustenna label.

15 Q. Then the next slide, in the last Dependent Claims -- no,  
16 they are the last ones.

17 Claims 11 and 14 of the '693 patent, what do those --  
18 what are those directed to?

19 A. Well, the first one says where the reinitiation dose of  
20 the PP3M is administered 30 days after the second reinitiation  
21 loading dose of PP1M. And Claim 14 basically just says the  
22 same thing, except now it says a month after administering the  
23 second reinitiation dose.

24 Q. Is it your opinion that those claims are obvious as well?

25 A. Yes, they're obvious. It was obvious from the same prior

United States District Court  
District of New Jersey

**Appx02448**

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

Plaintiffs,

vs.

CIVIL ACTION NUMBER:

2:20-cv-13103-EP-LHG

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

Defendants.

BENCH TRIAL VOL. 4

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
December 5, 2022  
Commencing at 10:00 a.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
                         UNITED STATES DISTRICT JUDGE**

1 Q. And for anybody following along later, this is slide 14 of  
2 your demonstrative deck, right, Dr. Sommi?

3 A. Right.

4 Q. Okay.

5 So Dr. Forrest relied on JAMA for a couple different  
6 purposes, right?

7 A. Right.

8 Q. So if we go back to the slide, Dr. Forrest's slide 15,  
9 which happens to also be our slide 15, magically, if we go back  
10 to that, and focusing on the last two bullet points, now that  
11 we've looked specifically at NCT423 and JAMA, does anything in  
12 those references suggest going in the other direction, that is  
13 going back to PP1M after a patient had already been advanced to  
14 PP3M?

15 A. No.

16 Q. So in terms of what's taught by the PP3M prior art, JAMA  
17 and NCT423, how does that compare to Claim 5 of the '693  
18 patent?

19 A. So we don't get -- there's nothing in there about a missed  
20 dose regimen for PP3M. There's nothing that identifies the  
21 four- to nine-month population, there's nothing about going  
22 back to PP1 after you've advanced a patient to PP3M. And  
23 there's nothing that says that you don't stabilize the patient  
24 on four or more months of PP1M before going to PP3M.

25 Q. So the other purpose or other reason that Dr. Forrest



1 relied on JAMA was to look at figure 2A, right?

2 A. Right.

3 Q. Do you have that?

4 A. Yes.

5 Q. That's on our slide 17.

6 Now, Dr. Forrest suggested that you could use  
7 figure 2A from JAMA to somehow identify the back end of that  
8 intermediate window, meaning that nine-month date for PP3M,  
9 right?

10 A. That's what he's suggesting.

11 Q. Do you agree with Dr. Forrest that a POSA would have  
12 adopted his approach that he testified about for extrapolating  
13 a missed dose window from figure 2A of the JAMA reference?

14 A. No.

15 Q. Let's start -- is figure 2A, does that reflect an interim  
16 or a final analysis?

17 A. So this is the interim analysis for JAMA.

18 Q. Did JAMA provide the same kind of graph for the final  
19 analysis?

20 A. They did, right below this one.

21 Q. Do you recall that Dr. Forrest testified that a POSA would  
22 rely on the interim analysis in JAMA and not the final  
23 analysis?

24 A. I do.

25 Q. What was your reaction to that?

1 A. I was kind of astounded that he would make that statement,  
2 that you wouldn't say that you would actually use all the data  
3 from a study.

4 Q. So can you explain to us then, what is the significance of  
5 an interim analysis in a placebo versus active drug study?

6 A. Right. So when we're doing relapse prevention trials in  
7 patients with schizophrenia, we put them on a placebo. And  
8 when we put somebody on placebo, they no longer get their  
9 medicine. And we know that there's a risk of relapse, and so  
10 when there's a risk of relapse, we have to do this -- we create  
11 a committee that tries to manage that because we don't want  
12 people to relapse any more than is necessary. So from an  
13 ethical point of view, you take a peek at the data at the  
14 prescribed time --

15 Q. Do you recall the prescribed time?

16 A. That was after 42 relapses.

17 All right. So you take all the relapses that  
18 happened in the studies -- and they felt from a statistical  
19 point of view that once the 42nd patient had relapsed, let's  
20 look at the data and if the study is positive, that's good  
21 enough. We don't have to keep people on placebo and allow  
22 those to relapse because relapse is a bad thing.

23 Q. Does that mean that at that point, the study stops at the  
24 interim analysis?

25 A. Well, so on the 42nd relapse, that's when the data

1 committee gets together, they do the analysis, they make a  
2 decision. Once the decision is made, then they -- if the study  
3 is positive, then they send the message out to the  
4 investigators saying the study is positive, it's time to get  
5 all your patients figured out and patients come in over the  
6 course of the year.

7 We don't just take 160 patients and suddenly put them  
8 on the drug. They're in over a period of time, so these people  
9 are working their way through the study.

10 So as an investigator -- I mean, I've done this many,  
11 many, times. When they say the study is over, it may take  
12 three, four, five, six months to get all the patients out of  
13 the study safely.

14 Q. And during that additional time, are you still collecting  
15 data?

16 A. We're still collecting data.

17 Q. Would a POSA disregard that additional data and try to  
18 extrapolate it?

19 A. I certainly wouldn't.

20 Q. Let's go back then to figure 2A from JAMA.

21 Okay. What does JAMA teach explicitly about the  
22 median time to relapse and what did Dr. Forrest testify he  
23 would extrapolate to use in his theories?

24 A. Right. So the -- so JAMA had the end point of the time to  
25 median relapse for 50% of the population. So that was 42

1 relapses. Right? And that's -- so these are what are called  
2 Kaplan-Meier survival curves. And so a perfect drug, the line  
3 would go all the way across one, nobody ever relapses. But as  
4 the person relapses, that line goes down and every relapse  
5 makes the line go down further.

6 And so once that line crosses 50% -- so we know the  
7 blue line never crosses 50% -- but the placebo line, the  
8 orangey line crosses 50% at 274 days, so they reported the  
9 median relapse at 50% is 274 days.

10 Q. When you say "they reported," who reported that the median  
11 relapse was 274 days?

12 A. The authors of JAMA.

13 Q. And what did Dr. Forrest testify at trial last week he  
14 would extrapolate?

15 A. He used the figure of 180 days.

16 Q. Okay. It's a little bit confusing about the timing and  
17 the significance of what 274 days actually means.

18 So can you explain to us what 274 days means in the  
19 context of Claim 5 of the '693 patent, meaning what's the time  
20 from the last dose of PP3M?

21 A. Right. So let's go back to this scheme where I have all  
22 the injections.

23 All right. So the text to Claim 5 talks about since  
24 the last injection. All right. And so Dr. Forrest is using  
25 the placebo group as the example for the missed dose. But when

1 you look at where the time, where the clock starts running in  
2 the data analysis, it's right where the blue -- the first blue  
3 and gold syringe is, right? That's time zero on 2A.

4 But their last injection was three months prior to  
5 that, so we need to account for that time, that three months.  
6 Right? And so when we look at the interim and final analysis,  
7 you see that the median time to relapse for the interim  
8 analysis is 274 days, which is about nine months, plus the  
9 three months, or about 12 months. And then for the full  
10 analysis, it's 395 days, which is about 13 months, plus the  
11 three months, you get to 16 months.

12 So using that strategy, one would have concluded it's  
13 somewhere between 12 and 16 months since the last injection.  
14 And that teaches away from nine months.

15 Q. If a POSA assumed, as Dr. Forrest does, that the JAMA  
16 publication could be used to suggest anything in terms of  
17 developing a missed dose regimen for PP3M, what would it  
18 suggest?

19 A. That you're going to go for 12 to 16 months. You wouldn't  
20 have -- the back end whereby somewhere between 12 to 16 months.  
21 It would teach away from the claim of nine months, the back end  
22 of the claim of nine months.

23 Q. And again, the 274 days, which calculates to be at least  
24 12 months, the time that the author said was the median time to  
25 relapse, and based on actual clinical data, did Dr. Forrest use

1 that and rely on that in his testimony?

2 A. He did not.

3 Q. All right. Let's see now. If we go back to figure 2A.

4 I want to go back to make sure that we got everything  
5 on the transcript right.

6 A. Okay.

7 Q. When you said -- when you testified a minute ago that if  
8 you could take anything away from the JAMA publication, that it  
9 would teach 12 to 16 months as the back end, then you said  
10 something about it -- something away or --

11 A. It teaches away from nine months.

12 Q. I think it got transcribed as takes away. No problem.

13 Okay. All right. So if we go back to figure 2A of  
14 JAMA, using this figure -- okay -- what did Dr. Forrest testify  
15 that the POSA would extrapolate to be the median time to  
16 relapse?

17 A. One hundred eighty days.

18 Q. That was his trial testimony. What did he testify in his  
19 deposition?

20 A. Two hundred seventy-four days.

21 Q. Now, would a POSA have used Dr. Forrest's approach to  
22 extrapolate the back end of this intermediate missed dose  
23 window for PP3M from figure 2A of JAMA?

24 A. No.

25 Q. Did Dr. Forrest attempt to use figure 2A of JAMA to

1 extrapolate the front end of the dosing window for PP3M?

2 A. No.

3 Q. What would happen, what would have happened if he had  
4 tried to do the same kinds of extrapolation for the front end  
5 of the missed dose window?

6 A. Well --

7 MR. SODERSTROM: Objection, Your Honor.

8 I don't believe that Dr. Sommi has ever opined on  
9 this particular equation as an expert before.

10 MS. MULLIN: He's showing what Dr. Forrest did not  
11 do. He didn't know what Dr. Forrest was going to say until his  
12 testimony. I think it's fair to point out that in his  
13 testimony, Dr. Forrest was selectively applying different  
14 theories all over the place. So he used one theory to get to  
15 this end of the four- to nine-month window. He disregarded  
16 that theory for something else and he used a different theory  
17 to try to get to the other window and he disregarded it for  
18 other purposes. I think that's fair --

19 MR. SODERSTROM: I think that's a different question  
20 than what Dr. Sommi would do in interpreting, I suppose, a  
21 front end of a window that he has never opined on. And I  
22 suppose if it's in his expert report --

23 MS. MULLIN: Well, I suppose if Dr. Forrest's expert  
24 report -- if he did this analysis that he was going to come to  
25 testify at trial, then Dr. Sommi would have responded to that.

1 MR. SODERSTROM: I think -- and we'll talk about this  
2 later --

3 THE COURT: I'm going to interject. I'm going to  
4 overrule you. I'm going to allow him to testify.

5 MS. MULLIN: Thank you, Your Honor.

6 BY MS. MULLIN:

7 Q. What would happen if Dr. Forrest had used the same  
8 analysis to estimate the front end of the intermediate dosing  
9 window for PP3M, the one that is in his extrapolation theory  
10 for the back end in figure 2A?

11 A. Well, I'm not sure what Dr. Forrest would have concluded,  
12 but if I looked at it, I would say you're basing the whole  
13 notion of establishing the window when somebody relapses, you  
14 would have to at least look at the period of time when there's  
15 almost no difference, right, which is about -- if you look at  
16 the -- Your Honor, if you look at -- over there, I'm going  
17 to -- there we go. Right around here is -- and I'm sorry for  
18 the shakiness, but it's -- you know, you would have to be about  
19 90 days or three months out, right, before you start seeing a  
20 significant amount of relapse. And then you add the three  
21 months to that and say, okay, so probably around six months  
22 would be the open -- would be the first window.

23 But that's how I would look at it. I wouldn't do  
24 that, but if I was going to do -- if I were -- if I was going  
25 to do it, I would say, you know, you're good to go for at least



1 six months.

2 Q. Okay. The final reference for PP3M that Dr. Forrest  
3 relied on was the 2014 press release, right?

4 A. Yes.

5 Q. And what is that generally directed to?

6 A. It's a press release about the JAMA study. It's just that  
7 the study was stopped because it became -- it was a positive  
8 study.

9 Q. Does JAMA or -- I'm sorry. Forgive me.

10 Does the 2014 press release suggest anything about  
11 whether or not patients have to be stabilized with Invega  
12 Sustenna prior to receiving PP3M?

13 A. It does. It mentions that the study subjects were first  
14 stabilized on Sustenna and then -- which is PP1M -- before  
15 moving to PP3M.

16 Q. So does this add anything to the JAMA or NCT423 references  
17 we've already discussed?

18 A. No.

19 Q. Okay. So let's see if we could wrap up the three  
20 references that mention PP3M that Dr. Forrest relied on, okay?  
21 And that's the NCT423, JAMA and the 2014 press release.

22 A. Right.

23 Q. Do you recall him relying on any other references that  
24 mentioned PP3M?

25 A. No.

1 So can you continue to explain what Dr. Forrest did?

2 A. So with what he was saying -- sorry.

3 What he was saying was at what point in time after  
4 the injection do you reach this threshold of 7.5 nanograms per  
5 mill and that was the threshold that he used. And this was his  
6 attempt to validate all of the previous findings and he found  
7 that it was about nine months.

8 Q. Okay.

9 If he had simulated the 525 mg equivalent dose of  
10 PP3M, where would you expect if you could make any -- expect  
11 anything with reasonable expectation that it was right, where  
12 would you think that that line --

13 A. When would it cross the 7.5-milligram --

14 Q. That's correct.

15 A. It would be at some point in time after the nine months.

16 Q. So following Dr. Forrest's analysis, if he actually  
17 simulated the 525 mg equation dose, could he have said a ha,  
18 that's what gets me to nine months?

19 A. I don't know how he would do that.

20 Q. Would it be something past nine months?

21 A. Yes.

22 Q. If he had done the smaller doses of PP3M, would it be  
23 sooner than nine months?

24 A. Yes.

25 MS. MULLIN: Okay.

1 Is that right?

2 A. I didn't opine on that. I don't have the -- I'm not a  
3 lawyer, so I don't know what all that means.

4 Q. Okay. Well, we went through this at your deposition.

5 You'll agree that a good number of paragraphs in the  
6 '693 patent are identical or nearly identical to paragraphs  
7 from the '536 publication, right?

8 A. I remember reading all of those word for word.

9 Q. If you need to again, but for recordkeeping's sake today,  
10 I do want to walk through a few of those.

11 For example, under the background of the invention,  
12 if you look at paragraphs three through six of the '536  
13 publication at DTX-97.0008, those are nearly identical to the  
14 paragraphs from column one, line two to line 67 of the '693  
15 patent, right?

16 A. Do you want me to review these like I did in my deposition  
17 or would -- because I did highlight the differences?

18 Q. If you recall what those differences were to the extent  
19 there were any from the deposition, then you could point those  
20 out. If you recall your ultimate conclusion from your  
21 deposition, that's fine, too.

22 A. Yeah, I mean there are minor differences between the two.

23 Q. Minor differences, you just mean two or three words here  
24 or there; is that fair?

25 A. So for instance, on 005, it talks about paliperidone

1 palmitate and then 45, it specifies three month paliperidone  
2 palmitate. I think that's consistent all the way through.

3 Q. Largely the same though, is that right?

4 A. Largely the same.

5 Q. And then in paragraph nine of the '536 publication, the  
6 last line provides the objective of the application to provide  
7 a dosing regimen of paliperidone palmitate for patients who  
8 have missed the monthly maintenance or stabilized dosing  
9 regimen of paliperidone palmitate, right?

10 A. Well, I would say that the words there are the same, but  
11 the scope of the 009 paragraph seems to be a little bit bigger  
12 than just the missed dose.

13 Q. Fair enough. I appreciate that.

14 But I'm really just looking at that last line of  
15 paragraph nine of the '536 publication and comparing that to  
16 column two, lines 25 through 29 of the '693 patent, and they  
17 say the same except one is for patients who miss PP3M, one is  
18 for patients who miss PP1M, right?

19 A. Yeah, I would agree that the objective of coming up with a  
20 missed dose regimen is in both.

21 Q. Just a few others. I won't belabor this. But if we look  
22 at paragraphs 50 and 51 of the '536 publication at DTX-97.12,  
23 this is identical or nearly identical to columns nine, lines  
24 eight through 35 on the '693 patent, right?

25 A. The molecule? What am I looking at? The paliperidone

1 esters are a psychotic agent?

2 Q. That's right. Paragraphs 50 through 51 of the '536  
3 publication and from the '693 patent, lines eight through 35.

4 A. I would agree with that. I'm not going read it to Sara.

5 Q. We went through a number of these at your deposition. You  
6 would not be surprised that there are a number of paragraphs  
7 between the '536 publication and the '693 patent that are  
8 nearly identical, right?

9 A. I would agree.

10 Q. And that is because both the '536 publication and '693  
11 patent relate to paliperidone palmitate long-acting injections  
12 and what to do when a patient misses a dose, right?

13 A. Sure.

14 Q. All right.

15 Looking at the '536 publication at DTX-97.0011 and,  
16 in particular, paragraphs 42 through 47, this describes what to  
17 do when a PPlM patient misses a dose and was last administered  
18 a dose four to six weeks ago, six weeks to six months ago, and  
19 more than six months ago, right?

20 A. Right. Those are the three embodiments.

21 Q. Of the '536 publication, right?

22 A. Of the '536 publication.

23 Q. So again, it's split into three windows, just like the  
24 '693 patent was, right?

25 A. I don't know about just like. I don't know if I agree

1 with that, but they are split into three windows.

2 Q. That's all I'm trying to say. There are three windows in  
3 the '536 publication with respect to patients on PP1M missing a  
4 dose, and there's three windows in the '693 patent with respect  
5 to PP3M patients missing a dose, right?

6 A. Right.

7 Q. So if we look at paragraph 43, first, this is addressing a  
8 patient that misses a dose and was last administered one  
9 between six weeks to six months ago, right?

10 A. Yes.

11 Q. It says in here that the reinitiation regimen may comprise  
12 a first loading dose, a second loading dose, and a maintenance  
13 dose, right?

14 A. Right.

15 Q. Then in the middle of the paragraph, 43, there at this  
16 prior art tells a POSA that the first dose and the second dose  
17 may depend on the stabilized dose prior to the missed dose,  
18 right?

19 A. That's what it says.

20 Q. And then just at the bottom there, there's another  
21 example. It starts with by way of another example, in here,  
22 this Janssen prior art is disclosing that for a missed dose  
23 that would have been 234 milligrams, that the first and second  
24 reinitiation doses should be 156 milligrams.

25 Right?

1 Q. If we turn to DTX-8.82, this is an information disclosure  
2 statement that Janssen submitted with respect to the '693  
3 patent, right?

4 A. Right.

5 Q. The applicant listed some U.S. and foreign patent  
6 documents first, and then at the bottom box, there's non-patent  
7 literature documents, right?

8 A. Right.

9 Q. The only one there is Osborne; is that correct?

10 A. Yes.

11 Q. There's no mention of the Sustenna label, right?

12 A. No.

13 Q. There's no JAMA?

14 A. There's no JAMA? You mean --

15 Q. There's no article -- the JAMA article that --

16 A. The one we referred to as JAMA?

17 Q. I'm sorry?

18 A. The one that we referred to as JAMA?

19 Q. Yes, fair point.

20 There's not the article that we've referred to as  
21 JAMA listed in that information disclosure statement, right?

22 A. I don't think JAMA was even published at that point. Yes,  
23 it was. No.

24 Q. You do understand that JAMA is prior art in this case?

25 A. Yes, I was looking at 2012. I was thinking JAMA started

1 back-end window, right?

2 A. Sure. So then you reject this whole hypothesis.

3 Q. All right.

4 Under your hypothesis, you were asked today from  
5 looking at JAMA where you would start and end potentially a  
6 middle window and you testified that you would start in at  
7 least six months and go to 12 to 16 months.

8 Do you recall?

9 A. That I would do that?

10 Q. Your counsel asked you, in reading JAMA, were you -- if  
11 you were to interpret JAMA to provide an end spot for the  
12 middle window, where would it be? And you testified probably  
13 12 to 16 months.

14 Do you recall that?

15 A. So the question had to do with if you accepted all the  
16 assumptions that Dr. Forrest does in terms of using that data,  
17 and you use all the data, you would come up with a -- and you  
18 use the end points that the authors used and not one that you  
19 thought was different or made you feel better or something,  
20 then you come up with 12 months, the nine months plus three  
21 months, or 16 months, the 13 months plus the three months.

22 Q. And then you said on the front end, in your opinion, with  
23 the same caveats you just provided, it would start at six  
24 months, right?

25 A. Well, if you look at, as we just did a little bit ago, the



1 relapse rates, when do people start to relapse, it's a few  
2 months after randomization, which is a few months after three  
3 months. So three months plus a few months, you could do your  
4 own interpretation, six months, five months. Doesn't get you  
5 to four months.

6 Q. No, but if it was five or six months to 12 to 16 months,  
7 as you've just discussed, that would -- there's overlap with a  
8 portion of the four- to nine-month window from Claim 5, right?

9 A. It doesn't get you to four months.

10 Q. My question is, it would overlap, right?

11 A. Sure.

12 MR. SODERSTROM: I don't have anything further.

13 THE COURT: Thank you. Any redirect?

14 (REDIRECT EXAMINATION)

15 BY MS. MULLIN:

16 Q. Very brief, Dr. Sommi.

17 I don't know if we have it ready to go, but I think  
18 Mr. Soderstrom pointed you to paragraph 62 of your opening --  
19 or of your expert report that was responsive to invalidity  
20 issues.

21 Do you recall that he started the day pretty much  
22 there?

23 A. Okay.

24 Q. He pointed you to the statement where you said that you  
25 relied on Dr. Gobburu's opinions, right?

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

Plaintiffs,  
vs.

CIVIL ACTION NUMBER:

2:20-cv-13103-EP-LHG

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

BENCH TRIAL VOL. 5

Defendants.

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
December 6, 2022  
Commencing at 10:00 a.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
                         UNITED STATES DISTRICT JUDGE**

1 nine-month target patient population?

2 A. Only as obvious, not as anticipating it.

3 Q. So I understand that you also had extrapolation theories  
4 and we will get to those. But trying to shortcut going through  
5 all the prior art references individually, I'm going to ask  
6 just one more time.

7 Okay?

8 A. Okay.

9 Q. In your direct testimony, did you identify any prior art  
10 reference as disclosing the four-to-nine-month target patient  
11 population?

12 A. Not directly.

13 Q. In your direct testimony, did you identify any prior art  
14 reference as disclosing using PP1M after a patient had been  
15 advanced to PP3M?

16 A. Not directly.

17 Q. In your direct testimony, did you identify any prior art  
18 reference as disclosing using PP3M without first stabilizing  
19 the patient on PP1M for at least a few months?

20 A. I'm sorry. You said without -- let me make sure I  
21 understood that question correctly.

22 Q. Sure.

23 In your direct testimony, did you identify any prior  
24 art reference as disclosing giving a dose of PP3M without first  
25 stabilizing the patient on PP1M for at least a few months?

1 A. Yes, the prior art disclosed PP1M prior to PP3M.

2 Q. The prior art disclosed PP1M prior to PP3M, but my  
3 question is did the prior art disclose giving PP3M without  
4 first stabilizing the patient on PP1M for at least a few  
5 months?

6 A. Okay. I'm sorry. I misunderstood.

7 Yes, they were stabilized on PP1M first.

8 Q. There was no reference -- prior art reference -- that you  
9 relied on in your direct as disclosing giving PP3M without  
10 first stabilizing the patient on PP1M for at least a few  
11 months.

12 Did I understand that correctly?

13 A. Correct. They were stabilized or given paliperidone  
14 palmitate prior to the PP3M.

15 Q. Okay.

16 Now, in your direct testimony, you put a lot of  
17 emphasis on the JAMA reference, right?

18 A. That was part of the art I analyzed.

19 Q. You testified that the fact that Janssen didn't provide  
20 JAMA to the patent office impacted your analysis a great deal.

21 Do you recall that testimony?

22 A. Yes, I recall it, as I said, that I considered that part  
23 of -- let me raise my microphone. I'm bending down to speak.

24 THE COURT: Can I take a minute? I'm having issues  
25 with my --

1 Q. Okay. JAMA tells us that the median patient will relapse  
2 12 months after their last dose of PP3M, right?

3 A. It tells us a range of patients and confidence interval  
4 about that. The median was, yeah, about 274 days since that  
5 missed dose, which would be about 12 months since they had  
6 their last dose.

7 As I explained during my direct, too, there's quite a  
8 confidence interval around that, too. But the median is there.

9 Q. Dr. Forrest, at your deposition, page 164, line 21, to  
10 165, line four, I asked you the question, "But what this is  
11 telling us is that the median patient will relapse 12 months  
12 after their last dose of PP3M."

13 And you answered, "Right"?

14 A. Yes, that's what we've just been saying. Nine months  
15 since their last -- 12 months since their last dose, nine  
16 months since a missed dose. That's the reason I said I think  
17 we got confused back and forth in your deposition, but I think  
18 you summarized.

19 Q. We were confused during your deposition, but last week  
20 when you were testifying, you put up your slide 40 -- you could  
21 look at that -- and you testified about how you could look at  
22 figure 2A from JAMA and that there was a natural jump from 274  
23 days back to 180 days, right?

24 A. Well, it's an interval. As I said during my direct  
25 testimony, 274 days, which is a year, we see that up to 80% of

1 the patients, anywhere from 30 to 80% of the patients have  
2 relapsed, and that's quite problematic, and so a POSA wouldn't  
3 want to wait that long. It would be much more in line to look  
4 at dosing interval before this, before the median, and actually  
5 it's very similar to what they did in the Sustenna label, too,  
6 when they were figuring it when did their own Kaplan-Meier plot  
7 there, too. So you look, you know, at a dosing interval before  
8 you have possibly over half your patients failing.

9 Q. That 180-day number that you testified about in trial did  
10 not appear in your expert report or your deposition, right?

11 A. I don't -- well, 180? Well, I discussed nine months, I  
12 believe, and how one arriving at this would come at nine  
13 months. So as I said, there was quite a bit of confusion  
14 during our deposition when we were talking about the days  
15 because at one point we were -- it's two ships sailing in the  
16 night where I was talking about months, you were talking about  
17 other months. That's the reason I'm trying to clarify. I  
18 think we reached that point at the end.

19 Q. Let me ask you point blank: Did you put that 180-day  
20 number in your expert report or deposition?

21 A. One hundred eighty month number, I said nine months. That  
22 is 180 days when you use a 30-month day.

23 Q. Let's back up, Dr. Forrest.

24 When we were at your deposition, you told me that 274  
25 days was the median time to relapse and that would be the time

1 that you would start over de novo, right? The patient's  
2 essentially naive to the drug.

3 That's what you told me in your deposition, right?

4 A. Well, okay, again, we're switching here whether -- I said  
5 that was the whole point during the deposition. There was  
6 confusion when we were talking about nine months since the  
7 missed dose and nine months since the last dose. That's why I  
8 was trying to clarify for you.

9 Q. Right. You were confused and latched on to that  
10 nine-month dose. After we took a break, you came back and said  
11 well, actually, the time to relapse is twelve months.

12 Is that what happened during deposition, Dr. Forrest?

13 A. No, I believe you were asking me the questions on that and  
14 then you were switching back and forth with a figure, also.  
15 And as I said, there was just a problem with the discussion of  
16 how that was going, and then we worked it out. It's that we  
17 just had -- it could be a little confusing, you know, as I told  
18 you, explaining to others what they're displaying here in JAMA  
19 because they're interested in time to missed doses, and they  
20 draw this summary conclusion here on 12 months, but then they  
21 actually, as I said, a POSA would actually look at the real  
22 data that was here, and as I tried to explain in my direct, you  
23 need to recall to add 90 days to all those. So, that was the  
24 whole point I was trying to clarify for you.

25 Q. At your deposition, you added 90 days to 274 days, and in

1 56.

2 BY MS. MULLIN:

3 Q. At your deposition, page 248, line nine to 249, line  
4 seven, I asked you the question, "And if you applied it to the  
5 back end, you would get to about 18 months, or about 540 days."

6 You said yeah.

7 You're replying that, of course, as I discussed in my  
8 report, would see there it would be potentially that long.

9 Right?

10 A. Yes. Then I explained JAMA.

11 Q. You have to optimize that 18 months, right?

12 A. It's looking at all the available prior art.

13 Q. You'll agree with me at least that if we applied the logic  
14 that you use for the front end window of the reinitiation  
15 period to the back end window, we would end up with a back end  
16 window date of 18 months, right?

17 A. In a void of not having JAMA, yes, you could arrive up to  
18 that.

19 Q. I'm asking you just arriving at that. We've talked about  
20 JAMA, I'm sure you'll talk about it more on redirect.

21 The question is: If you used the same logic that you  
22 applied to estimate the front end of the missed dose window and  
23 you applied that exact same logic to the back end, what you  
24 would get for the back end would be 18 months, right?

25 A. In a void, yes.



1 points. You use all the data you had at hand.

2 And then during my early -- when I wrote my reports,  
3 there was a question if JAMA would even be allowed and I also  
4 discussed that there's other ways even without JAMA you could  
5 get some of these data, such as just a PK modeling is another  
6 approach. I said you could use also PK modeling.

7 Q. Did I just hear you say that you would use all the data  
8 available?

9 A. You would use -- yes, quite a bit of the data available.  
10 You would put the appropriate weight on each one and understand  
11 which is most relevant, but you would use data that is  
12 available.

13 Q. But you would not use the final analysis from JAMA? You  
14 would disregard any additional data there and rely on the  
15 interim results, right?

16 A. Because JAMA told us to ignore that data -- I'm sorry --  
17 those data.

18 Q. Is there actually a place in JAMA where JAMA says ignore  
19 any data that we collected and analyzed and concluded to extend  
20 the PP3M protection from relapse even much longer? Did JAMA  
21 say just ignore that, everybody, or did they report it?

22 A. You report all the data from your trials, but then you  
23 tell what you need to actually look at. And they told us the  
24 data you should analyze is the interim analysis.

25 Q. Did they say the data you should analyze is the interim

1 Q. Okay. So let's go back for a second because in the  
2 claimed dosing regimen, I think this is showing slide 32, after  
3 a patient received a dose of PP3M, if they come back within  
4 four to nine months, the first step of the claimed missed dose  
5 regimen is give them PP1M, right?

6 A. That is correct.

7 Q. And I asked you at least four times in your deposition if  
8 there was any prior art directed to giving a dose of PP1M after  
9 a patient had been advanced to PP3M and you couldn't identify  
10 any, right?

11 A. As I said, the prior art just teaches giving PP1M, then  
12 PP3M.

13 Q. So you have given the opinion that a POSA developing a  
14 treatment for a patient that missed a dose of PP3M would give  
15 them PP1M because it might be a faster-acting formulation,  
16 right?

17 A. It's faster acting and it's an approved product that had a  
18 known -- could be used to initiate a patient and reinitiate.

19 Q. Well, when I asked you at your deposition, at least six  
20 different times, whether anything in the prior art demonstrated  
21 that PP1M reaches therapeutic levels any faster than PP3M, you  
22 could not identify anything, right?

23 A. Well, we didn't finish that line of questioning before you  
24 ended the deposition, but it did not -- if your question is did  
25 anything identify PP1M could be used -- or PP3M could be used

1 A. The Kaplan-Meier curve.

2 Q. For JAMA?

3 A. Yes.

4 MR. SODERSTROM: It's at six, I believe, Scott.

5 THE WITNESS: It would be the top one.

6 I hope, Your Honor, most of this has been clear, the  
7 way I'm trying to explain this. The graph is difficult.

8 THE COURT: Don't worry about me.

9 THE WITNESS: But, you know, as I explained numerous  
10 times at 12 months, which would be if you follow that line that  
11 says 274 days, the median patients have failed.

12 And as I said, a POSA would want to look well before  
13 that, at dosage before that, before the median patient failed,  
14 and they'd understand this for multiple methods, such as I  
15 discussed modeling. But also the Sustenna label, too, they  
16 would understand it from this. Because if you looked at it as  
17 I was describing to opposing counsel in the Sustenna label,  
18 they have a Kaplan-Meier plot and it, too, in figure one of the  
19 label, if Scott could --

20 MR. SODERSTROM: Scott, are you able to pull up  
21 DTX-25.46 to 47? Actually, we could start with 47. DTX-25.47.

22 THE WITNESS: So this is the same study. They also  
23 did a missed dose study. They plotted the data upside down.  
24 Instead of starting from 100 and, you know, reporting which  
25 fraction of patients were still good, they reported which

1 fraction failed. So just understand you have to flip it on its  
2 head.

3 But you see here that at 163 days since they  
4 randomized, which, this case, you need to add 30. I'm sorry.  
5 That's where it gets confusing because it was 30 days since  
6 they missed their dose, because this is the Sustenna, the PP1M  
7 product. Well, you see that, you know, at 193 days, based on  
8 that, this is where most patients failed. The study looked one  
9 dosage interval before that, which was six months in this case,  
10 when they placed that you should start to treat patients in de  
11 novo.

12 And so if you apply that same logic when looking at  
13 the PP3M, the JAMA, again you see the median fails at the point  
14 in time, 274 days, which is equivalent to 12 months in its case  
15 since patients had their last dose. So you look one dosage  
16 interval before that and you get nine months in this case when  
17 you start to think about putting patients on a stronger  
18 reinitiation regimen, which would be treating them as de novo.

19 So it's the same logic there, too.

20 BY MR. SODERSTROM:

21 Q. Just one more question to be sure.

22 If we go to 25.46, Scott, just the page before that  
23 describes this study.

24 Do you see the line during the double blind phase,  
25 patients were randomized to either the same dose of Invega

1 Sustenna they received during the stabilization phase --

2 A. Yes.

3 Q. -- or to placebo; is that right?

4 A. That's correct.

5 Q. Does that mean that prior to the randomization point at  
6 time zero, the patients were receiving some dose of Invega  
7 Sustenna?

8 A. They were stabilized, yes.

9 Q. Counsel also asked you questions regarding the front end  
10 of what we've referred to as the middle window being 4.2 under  
11 the calculation that you provided.

12 Do you recall that?

13 A. Yes, sir.

14 Q. You mentioned during that discussion that the start of  
15 that window, one would have more confidence I suppose in that  
16 number than the back end window. You asked to explain that. I  
17 don't think you had the opportunity to do so.

18 Can you explain what you meant by that?

19 A. A slight overshoot would not be problematic for a patient.  
20 I mean, for example, some of Samtani's later studies, like the  
21 2011 and '12, I believe, he also published on the PP1M, they  
22 actually looked at 150 150 regimens there. And the fact that  
23 the patient went slightly over was not problematic. They also  
24 saw in the '563 publication when patients went briefly over the  
25 maximum dose, it wasn't too problematic. They tried to

1 maintain them within the window. The real danger in all these  
2 was underdosing a patient and them relapsing.

3 Q. You were also asked questions in same sort of line about a  
4 POSA reaching 4.2 as the beginning of the window and 18 as the  
5 back end of the window and you said that that could be true, I  
6 think you said in a void or vacuum; is that right?

7 A. Yes, that's correct.

8 Q. Let's put the rest of your testimony aside for a minute.

9 4.2 to 18 months overlaps with four to nine months,  
10 right?

11 A. Yes, it does.

12 Q. You were asked questions on slide 13. I don't have these  
13 in electronic form, so perhaps if you have it with you from  
14 your cross binder there --

15 A. Yes, it's large print.

16 Q. Sorry?

17 A. It's large print.

18 Q. The question was, at the effective filing date, a  
19 half-life of PP3M was not known, and you said that it wasn't  
20 explicitly known and you said that you would like to explain  
21 that, but didn't get an opportunity.

22 Can you explain what you meant by that?

23 A. The '536 discusses a great deal about the dosing and  
24 half-lives, and they determined this journalization based upon  
25 all products, and they use this knowledge in designing their

1 dosage forms. So when they were designing their regimens too,  
2 they relied in part in this knowledge that depots generally  
3 have a half-life similar or administration interval similar to  
4 one to two half-lives for the products. It's general knowledge  
5 that they accepted and that they applied to their product too.

6 Q. And then we had some questions about the '536 publication  
7 being all about paliperidone palmitate.

8 MR. SODERSTROM: And, Scott, I don't know if you're  
9 able to pull up the direct Forrest slides, slide 25. Go one  
10 back. Go one forward. You were right.

11 BY MR. SODERSTROM:

12 Q. Dr. Forrest, this is the abstract for the '536  
13 publication; is that right?

14 A. Yes.

15 Q. Does it reference any other drug aside from paliperidone  
16 palmitate?

17 A. Yes, it -- this is part of what I was trying to clarify,  
18 that -- when I said it was all about the claimed subject matter  
19 and the predominance of the teachings. But it also teaches  
20 minor uses like switching from other drugs, and it teaches all  
21 that table three information we also talked about.

22 Q. Then if we just look at the title of that slide, and you  
23 might not be able to see it there, but the title of the '536  
24 patent was with respect to -- perhaps you're able to blow that  
25 up, Scott -- a dosing regimen associated with long-acting

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

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JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

Plaintiffs,  
vs.

CIVIL ACTION NUMBER:

2:20-cv-13103-EP-LHG

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

BENCH TRIAL VOL. 6

Defendants.

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
December 7, 2022  
Commencing at 10:00 a.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
                         UNITED STATES DISTRICT JUDGE**



1 MR. COHEN: No, that's not controversial and I'll ask  
2 Dr. Kohler what opinions he's providing today after he's been  
3 qualified as an expert.

4 THE COURT: Go ahead.

5 BY MR. COHEN:

6 Q. Dr. Kohler, what opinions are you prepared to provide  
7 today?

8 A. I'm prepared to speak on the importance of the missed dose  
9 instructions for Invega Trinza and the real world perspective  
10 and benefits of treating with Invega Trinza.

11 Q. Dr. Kohler, were you asked in this case to provide and are  
12 you here to provide today any opinion as to whether or not the  
13 claims of the '693 patent are valid or infringed?

14 A. No, I'm not.

15 MR. COHEN: Your Honor, I apologize.

16 The record might have been unclear based on the prior  
17 proffer. We move to qualify Dr. Kohler as an expert in the  
18 subject matters that I stated.

19 MR. MUKERJEE: Subject to what I said, we have no --

20 THE COURT: We have an agreement, gentlemen?

21 MR. MUKERJEE: Yes.

22 BY MR. COHEN:

23 Q. Let's start with schizophrenia.

24 We heard a lot about it in trial, but I want to give  
25 you an opportunity to tell us in your own words your

1 perspective on the illness, its care, the patients who you see  
2 and the doctors that they deal with.

3 A. Very briefly, schizophrenia is a condition that affects  
4 about 1% of the population in terms of lifetime prevalence. It  
5 has its onset during late adolescence and early adulthood,  
6 which are very important for a person's individuation and  
7 functioning.

8 The importance in treating people with schizophrenia  
9 early in the illness is to treat them to improvement, if not  
10 remission and recovery. That can be attained within the first  
11 let's say, five years, max ten years of illness. If that is  
12 not achieved, then the illness runs in chronic and overtime  
13 deteriorating course with a limited life expectancy. Even  
14 though schizophrenia has, as I said, a 1% lifetime prevalence,  
15 it's considered to be under the 12 most disabling conditions  
16 worldwide.

17 Q. In terms of doctors and patients with schizophrenia, how  
18 does the disease affect that relationship?

19 A. People who have schizophrenia may come to treatment in  
20 different settings: Inpatient settings, outpatient settings.  
21 It's important to forge a relationship and a plan for effective  
22 treatment. And effective treatment in schizophrenia, really  
23 the single-most important treatment is medication treatment.  
24 There are other very important elements of treatment that --  
25 but they depend on medication treatment to effectively control

1 symptoms.

2 Q. Is there a cure for schizophrenia?

3 A. There's no cure for schizophrenia. The medications in  
4 particular, antipsychotics medications, affect brain systems  
5 that use dopamine as a neurotransmitter and they attempt to  
6 reestablish a certain balance in the brain system that has been  
7 gotten out of whack or out of balance and, therefore, produces  
8 the psychosis symptoms.

9 Q. Is it important for patients suffering from schizophrenia  
10 to take their medicine?

11 A. It's very important for people to take their medicines,  
12 and many people early in the course of illness respond very  
13 well to antipsychotic treatment, only to stop treatment  
14 prematurely and suffer a relapse. And with repeated relapses,  
15 what happens is increasing disability and chronicity of  
16 illness.

17 Q. Those relapses, are the consequences of those permanent?

18 A. They are. People will respond less well to medications,  
19 people will have more side effects, and people, not necessarily  
20 as the result of treatment, will experience functional  
21 impairment and cognitive impairment.

22 Q. Do patients with schizophrenia in your experience  
23 generally adhere to their treatment regimens?

24 A. Adherence is a problem in all areas of medicine. It is a  
25 particular issue in the area of schizophrenia in that we know

1 that about 50% of people with, let's say, first episode  
2 schizophrenia stop medications within one year of being started  
3 on medications, but it remains a problem throughout the whole  
4 course of illness.

5 Q. So why would a patient with schizophrenia stop taking a  
6 medicine that's working?

7 A. There are different reasons. One is that the person  
8 disagreed that they have an illness. One is that the person  
9 responds well to treatment and thinks they, therefore, no  
10 longer need medication. They don't understand. That's similar  
11 to a hypertension. If let's say blood pressure is normal, that  
12 still means we have to take anti-hypertensive medication, so  
13 they stop antipsychotics and experience a relapse.

14 Another is side effects, in that people, especially  
15 those who are younger, experience medication side effects that  
16 are called acute extrapyramidal symptoms. The classic ones are  
17 painful muscle contractions in the neck, throat. The person  
18 may end up in the emergency room. It's very uncomfortable,  
19 distressing. Obviously a person may be reluctant to continue  
20 with medication.

21 Another side effect is the experience of restlessness  
22 in that a person cannot sit or lie still. Again, a particular  
23 side effects in the course of early illness that can lead to  
24 suicidality.

25 Q. If a patient experienced side effects from a medicine, how

1 does that relate to their willingness to continue treatment in  
2 the future?

3 A. In particular, a patient who has limited agreement about  
4 taking medication, it affects their assessment of the risk  
5 benefit of taking medications and, therefore, they will feel  
6 that the medication is too risky to continue taking.

7 Q. Is it important in the treatment of patients with  
8 schizophrenia to avoid potential side effects from over  
9 treatment?

10 A. It is.

11 Q. Is adherence any better -- we've heard a lot about  
12 long-acting injectables in this trial.

13 Is patient adherence to medication better with  
14 long-acting injectables than once-a-day pills?

15 A. We have to consider that patients who are good candidates  
16 for long-acting injectables are those who have shown for  
17 different reasons not to be able to take oral medications on a  
18 regular basis. Therefore, they would do poorly if just  
19 considered with all medication. By taking long-acting  
20 injectable medication, they are afforded a medication that  
21 lasts for a longer period of time. It doesn't take away the  
22 issue of non-adherence. They still have an opportunity to miss  
23 the medication.

24 Q. Do patients on long-acting injectable antipsychotics still  
25 nevertheless miss the regularly scheduled doses?

1 A. Yes, that is correct.

2 Q. Let's talk about Invega Trinza. That's why we're here.

3 We want to focus your attention right around the time  
4 Invega Trinza was approved, May 2015.

5 Were any of the long-acting injectable antipsychotics  
6 available prior to Trinza in once-every-three-month dosages?

7 A. No, they were not. There were several first-generation  
8 antipsychotics. Haldol and Prolixin. There was Risperdal  
9 Consta, Invega Sustenna, and Abilify Maintena. These were  
10 products that were given every two weeks to max five weeks.

11 Q. The products that were available before Trinza were  
12 available every two to five weeks.

13 In your opinion, was there a need for longer acting  
14 injectable antipsychotics?

15 A. There definitely was a need. Even though that one-month  
16 formulation covers the person for a one-month period, there's  
17 still the task of presenting either to the doctors or nurse's  
18 office or pharmacy. And in particular, for patients who do  
19 well on long-acting injectables and who have other activities  
20 and responsibilities to pursue in life, a product that lasts  
21 for longer than three months is of benefit.

22 Q. And now when Trinza was first approved, again, we're  
23 talking about May 2015 -- how was it received by the field?

24 A. When Invega was first approved, as a field, we had no  
25 experience with a product that would last three months, if not

1 longer. We had some concerns about the amount of medication  
2 necessary to treat a person for three months, whether the  
3 product would remain effective for three months and longer and  
4 also whether there could be -- because of the large amount of  
5 medication -- side effects that would emerge within maybe  
6 several weeks that we then would have to manage over the course  
7 of three months. And if they were severe, obviously the person  
8 would not continue taking Invega Trinza.

9 Q. Are potential side effects a bigger concern for products  
10 that last three months than products that are intended to last  
11 for shorter time periods?

12 A. Yes. And let's say we have an oral medication where a  
13 person experiences side effects. Half-life of these  
14 medications is typically short, so within several days, we  
15 could expect that the side effects would subside for the most  
16 part. If we're dealing with a three-month product, then we're  
17 faced with managing side effects over a much longer period of  
18 time.

19 Q. Can you -- once you give them a dose of three-month  
20 product, can you take the dose out if they're experiencing side  
21 effects?

22 A. No. We would have to administer medications to counter  
23 the side effects. In more extreme cases, people would need to  
24 be hospitalized.

25 Q. We've had about seven years of experience with Invega

1 to functional improvement and hopefully a more independent  
2 functioning. The three-month formulation frees them up to  
3 pursue these activities.

4 However, we have to consider that people who go on to  
5 long-acting injectables for different reasons have been shown  
6 to have a high rate of nonadherence. So nonadherence will  
7 occur again.

8 In the setting of missed dose or nonadherence, if you  
9 wish, we have to have clear instructions about how to catch a  
10 person up to the previously effective treatment regimen. We're  
11 not talking about people who are inherently unstable and who  
12 will be rehospitalized. We're talking about people where the  
13 continuation of Invega Trinza is necessary.

14 Q. How do the missed dose instructions contribute to your  
15 ability to use Invega Trinza with such patients?

16 A. The missed dose instructions are divided into three time  
17 periods. One that allows them to continue the previous Invega  
18 Trinza dose and having knowledge that based on what Janssen has  
19 found with respect to its studies, as well as what the FDA has  
20 approved, that the medication will continue to exert its  
21 efficacy.

22 The second time period is a period where there's some  
23 very specific instructions about how to catch a person up to  
24 previous treatment, which now includes going back to Invega  
25 Sustenna.



1 Invega Trinza.

2           So as a physician, I have the obligation to weigh  
3 risks and benefits of continued treatment. What that means is  
4 I do not want to experiment and undertreat the person and  
5 therefore the person may experience relapse. So I want to use  
6 the best available information to maintain the personal  
7 treatment.

8           On the flip side, I could err on the side of over  
9 administration, and now the person will have side effects which  
10 may preclude the person from continuing with medication.

11 Q. Now, have you treated or been involved in the treatment of  
12 a patient on Invega Trinza who had missed a dose and came back  
13 four to nine months after their previous dose?

14 A. Yes, I have.

15 Q. We heard earlier at this trial Dr. Berger testify that  
16 he's never used the four to nine month instructions and that he  
17 had residents who attempted to, but were unsuccessful at using  
18 it --

19           MR. MUKERJEE: Objection, Your Honor.

20           Dr. Berger's testimony that this Court has heard has  
21 all been related to non-infringing. This expert has already  
22 testified he's not offering opinions on infringement and he's  
23 not offering opinions on invalidity. He may debate what  
24 exactly these opinions are.

25           THE COURT: I want everybody to calm down.

1 any foundation that he's reviewed that transcript. So, in the  
2 absence of that --

3 THE COURT: The way I'm going to frame it is  
4 Dr. Berger was a treating psychiatrist and he's giving an  
5 example of what he -- he's giving an example of it. I'm going  
6 to allow it because it's only an example.

7 MR. MUKERJEE: Okay.

8 MR. COHEN: Thank you, Your Honor.

9 A. I believe the question was whether I was able to return  
10 people to treatment within the four to nine month period using  
11 the Invega Trinza missed dose instructions, and the answer is  
12 yes.

13 BY MR. COHEN:

14 Q. How many patients have you been involved with the  
15 treatment of using Invega Trinza?

16 A. I estimate that I've treated about 70 patients with Invega  
17 Trinza.

18 Q. How many of those patients have you treated according to  
19 the four to nine month missed dose instructions on the label?

20 A. I've treated about five patients.

21 Q. Have you ever returned a patient to Invega Trinza who had  
22 missed a dose in a manner that did not accord with the Invega  
23 Trinza label?

24 A. No, I cannot recall that.

25 Q. In your opinion, is it common for other health care

1 professionals to rely on the missed dose instructions on the  
2 Invega Trinza label?

3 A. In my experience, other health care providers rely on the  
4 missed dose instructions.

5 Q. Now, let's go back in time to when you were first  
6 considering whether or not to use Invega Trinza, whether or not  
7 to adopt it as part of your practice.

8 Did the missed dose instructions at that time that  
9 were reflected on the Invega Trinza label, and in particular,  
10 the four to nine month dose instruction, did they play any role  
11 in your consideration of whether or not to adopt Invega Trinza  
12 in your practice?

13 A. Yes, they did and for these two reasons, one is that  
14 again, we are dealing with a three-month product that we as  
15 clinicians have really limited knowledge about,  
16 pharmacokinetics, pharmacodynamics, how long the product lasts  
17 to exert clinical efficacy. So it was very important to have  
18 information if there's a missed dose.

19 And the other reason is that Invega Sustenna did have  
20 or does have missed dose instructions. Same with the other  
21 second generation, long-acting injectables. And therefore, if  
22 this were missing in Invega Trinza, I would have been very  
23 reluctant in transferring stable patients on Invega Sustenna to  
24 Invega Trinza. Now I'm -- yeah.

25 Q. You can continue if you weren't finished.

1 A. No. I just wanted to make a point about, again, when we  
2 look at five patients out of 70 patients, we're not looking at  
3 a large number, but these are people who were candidates for  
4 continued Invega Trinza treatment. The treatment nonadherence,  
5 of course, is a lot. With a long-acting injectable, of course  
6 it's a lot higher in Invega Sustenna.

7 Q. So what would the risks be if you were faced with treating  
8 a patient who had missed a dose of Invega Trinza and you didn't  
9 have the label instructions on how to reinitiate such patients?

10 A. The risks would be that while I'm aware that this product  
11 will likely last, or be in the body for longer than three  
12 months, I do not know how to catch a person up to treatment.  
13 Would I put the person back on oral medication? Now, the  
14 people on long-acting injectables already have had a poor  
15 experience with oral medications. Would I go treat the person  
16 with Invega Trinza without knowing whether that would  
17 sufficiently maintain the person? Or would I try to put  
18 together some regimen of Invega Sustenna which, again, we have  
19 never used a shorter acting long-acting injectable to catch up  
20 to a missed dose of a long-acting injectable so that we have --  
21 as clinicians, we have no experience doing that.

22 Q. Are you aware of any scientific literature that expresses  
23 similar concerns about patients who have missed a dose and how  
24 to treat them?

25 A. Yes.

1 Q. Do we have a slide about that paper as well?

2 A. Yes, I do.

3 MR. COHEN: Can we go to the next slide, please?

4 BY MR. COHEN:

5 Q. What was the general purpose of the -- first, can you  
6 identify the paper for us?

7 A. This is a review paper published in the journal of  
8 clinical psychiatry in 2016 with the first author being  
9 Christoph Correll. That includes eight experts in the field of  
10 schizophrenia and antipsychotic medications.

11 The particular focus of this article was on  
12 long-acting injectables, and the reason why the authors felt  
13 that penning this paper was important is because we know that  
14 in the United States, long-acting injectables are vastly  
15 underused in the population of schizophrenia, and they looked  
16 at the extant literature on what is known about long-acting  
17 injectables, and as part of that, they looked at why  
18 psychiatrists are reluctant to prescribe long-acting  
19 injectables.

20 Q. What did this group of eight experts in the field report  
21 about why physicians are reluctant to use long-acting  
22 injectables and how that pertains to missed dose instructions?

23 A. In their opinion -- and I would agree with that -- is that  
24 many clinicians really lack knowledge about practical issues  
25 with respect to long-acting injectables, including which dose

1 to select, pharmacokinetics, and what to do when a patient is  
2 late and experiences a missed dose or has persistent symptoms  
3 after starting therapy.

4 Q. So how does what the authors say in this paper relate to  
5 your opinion that the missed dose instructions are important to  
6 clinicians?

7 A. Again, it supports that I, as a clinician, am giving  
8 information that improves my confidence that I can continue  
9 treatment with Invega Trinza rather than experimenting to catch  
10 up after a missed dose.

11 Q. Dr. Kohler, would you be using Invega Trinza as often as  
12 you use it today if it came out without missed dose  
13 instructions on the label?

14 A. As I described before, I would have been really reluctant  
15 in continuing patients who were improved on Invega Sustenna on  
16 Invega Trinza. I would have remained with the Invega Sustenna  
17 product. At some point, but throughout the past seven years,  
18 I'm sure I would have used Invega Trinza; however, one has to  
19 consider I'm in a setting where we're very interested in using  
20 all medications that are available to see what is the impact in  
21 patients who we treat, the benefit. I think that in the  
22 overall community of psychiatrists, the hesitancy to adopt a  
23 product would have been greater than mine.

24 Q. Now to be clear, are the missed dose instructions the only  
25 reason that you would be -- that you're using Invega Trinza

1 today?

2 A. No, absolutely not. I mean the upfront benefits of Invega  
3 Trinza really are the effectiveness of treatment and tolerable  
4 side effects.

5 Q. But in your opinion, would Invega Trinza be as widely used  
6 as it is today if it lacked missed dose instructions?

7 A. I don't think it would be as widely used.

8 MR. COHEN: No further questions, Your Honor.

9 MR. MUKERJEE: Your Honor, in light of the kind of  
10 scope of the background information, if I could ask for just  
11 about five minutes because I might just retool my cross a  
12 little bit.

13 THE COURT: Take your five minutes.

14 MR. MUKERJEE: You'll be happy.

15 THE COURT: We'll be back.

16 (Time noted: 1:51 p.m.)

17 (Recess taken)

18 (Time noted: 2:01 p.m.)

19 THE COURTROOM DEPUTY: All rise.

20 THE COURT: Please be seated.

21 MR. MUKERJEE: Thank you, Your Honor, for that time.

22 It'll inure hopefully to the Court's benefit because what I was  
23 trying to do is cut things, not add.

24 (CROSS-EXAMINATION)

25 BY MR. MUKERJEE:

1 Q. And that was your answer, correct?

2 A. That was my answer, yes.

3 Q. Okay. Now, using Trinza for the treatment of bipolar  
4 disorder, well, that would be an off-label use, correct?

5 MR. COHEN: Objection, Your Honor.

6 This goes to infringement and Mr. Mukerjee made a big  
7 objection about Dr. Kohler testifying about what he thought was  
8 about infringement. It's unfair to be asking questions about  
9 infringement.

10 MR. MUKERJEE: All I'm asking him is if you use  
11 Trinza for bipolar disorder, is it in the label or is it not.

12 THE COURT: But that's a different question than what  
13 you posed, so I'm going to sustain the objection.

14 BY MR. MUKERJEE:

15 Q. Okay. If you use Trinza for bipolar disorder, would that  
16 be on the label?

17 A. That would be off-label use.

18 Q. That would be off-label, okay.

19 And on the topic -- just on off-label use, you've  
20 prescribed drugs outside of what information is contained in  
21 the label in your own practice, correct?

22 MR. COHEN: Objection, Your Honor.

23 Off-label use, Mr. Mukerjee is asking questions about  
24 infringement, which are outside the scope of his direct  
25 testimony.



1 Q. Okay.

2 Dr. Kohler, may I proceed then? Are you --

3 A. Yes.

4 Q. Okay.

5 Looking at each of these three doses -- so I'm  
6 talking about day one, day eight and a month out -- you agree  
7 they could be adjusted based on the clinical presentation of  
8 the patient, correct?

9 A. The way I understand the label is that the recommendation  
10 is not to adjust according to clinical situation.

11 Q. But you agree they could be adjusted based on clinical  
12 presentation of the patient, correct?

13 A. That would be an off-label use.

14 Q. Again, Dr. Kohler, that's not my question.

15 You agree that they could be adjusted based on the  
16 clinical presentation of the patient, correct?

17 MR. COHEN: Objection.

18 Asked and answered.

19 And also, this appears to be infringement  
20 cross-examination, not what Dr. Kohler testified about.

21 MR. MUKERJEE: The entire -- if there is any --

22 THE COURT: I believe he said it would be an  
23 off-label use. That's how he answered your question.

24 MR. MUKERJEE: Right.

25

1 BY MR. MUKERJEE:

2 Q. I think my question right now, though, is that you agree  
3 that they could be adjusted based on clinical presentations of  
4 the patient?

5 Again, there are no tricks here, Dr. Kohler. I'm  
6 asking you questions really literally that you were asked in  
7 your deposition.

8 MR. COHEN: Objection.

9 Asked and answered.

10 MR. MUKERJEE: I don't know if he answered that  
11 question, Your Honor.

12 THE COURT: I'll overrule. Let him answer the  
13 question.

14 A. My answer would be yes.

15 Q. You personally, Dr. Kohler, you wouldn't blindly follow  
16 the reinitiation regimen without assessing whether the patient  
17 is even eligible for the regimen, correct?

18 MR. COHEN: Objection, Your Honor.

19 This is outside the scope of the direct and directly  
20 inherent language from Mylan's infringement case, blindly  
21 following the label.

22 Mr. Mukerjee objected to my line of questioning  
23 vociferously that he believed we were going into infringement.  
24 This is absolutely unfair to go to infringement.

25 MR. MUKERJEE: Your Honor, this is from deposition

1 testimony that I'm quoting that was part of the question that  
2 he answered and I can put it up.

3 But again, his testimony is to discuss the real world  
4 implications of Invega Trinza. And the real world implications  
5 about following this particular dosage regimen, putting aside  
6 the fact that out of the thousands of patients, there's only  
7 five times that he's done it. But his proffer was the real  
8 world implications. This is a real world implication.

9 BY MR. MUKERJEE:

10 Q. If you have a patient now --

11 MR. COHEN: Your Honor, I maintain my objection. It  
12 goes to infringement. It's irrelevant to the issues Dr. Kohler  
13 testified to on direct.

14 And, furthermore, it's irrelevant that he testified  
15 at his deposition. Counsel asked wide-ranging questions at his  
16 deposition and the scope here is what Dr. Kohler presented on  
17 direct examination.

18 THE COURT: I'm going to sustain the objection.

19 MR. MUKERJEE: Okay.

20 BY MR. MUKERJEE:

21 Q. Okay. So going to your real world implications, you're  
22 familiar with the Invega Trinza label, right?

23 A. I am.

24 Q. In your practice, again, just bringing it to the real  
25 world, you've reviewed it?

1 A. Yes, I have.

2 Q. Your testimony is that you follow it, correct?

3 A. Yes.

4 Q. Okay. Now, you agree, though, in that section of the  
5 label -- and you've reviewed this section, correct?

6 A. Yes.

7 Q. You agree that there's nothing in this missed dose section  
8 that speaks to a section where the patient doesn't return for  
9 the day 8 second reinitiation dose; isn't that right?

10 A. That is correct.

11 Q. And that is the situation that can happen in the real  
12 world; isn't that true?

13 A. That can happen.

14 Q. Okay. This section is also -- and the section that you've  
15 reviewed here, this section is also silent about the situation  
16 where the patient doesn't return one month after the day eight  
17 injection.

18 You agree there's nothing in the missed dose section  
19 that speaks to this, correct?

20 A. Correct.

21 MR. COHEN: Objection, Your Honor. This line of  
22 questioning is, again, continuing to be about infringement.  
23 It's not --

24 THE COURT: Overruled.

25 Continue.

1 windows?

2 A. I can talk about the importance. I think when you're  
3 talking about the benefit of the time windows --

4 Q. You haven't distinguished between those time windows in  
5 any way, correct?

6 As to purported benefits, you haven't distinguished  
7 between them, correct?

8 You haven't offered any opinions in this case  
9 distinguishing any one of those windows as having any  
10 preferential benefit over the other; isn't that right?

11 A. I don't know if I did or if I didn't in my report.

12 Q. Okay.

13 So sitting here today, you don't recall giving that  
14 opinion; is that fair?

15 A. I don't recall giving that opinion before.

16 MR. MUKERJEE: Okay.

17 I have no further questions, Your Honor.

18 THE COURT: Redirect?

19 MR. COHEN: Thank you, Your Honor.

20 And based on Mr. Mukerjee's representation that none  
21 of his testimony will be used out of context to support Mylan's  
22 non-infringement defense, I only have very few questions.

23 (REDIRECT EXAMINATION)

24 BY MR. COHEN:

25 Q. Dr. Kohler, you were asked a couple of questions about the

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

Plaintiffs,

vs.

CIVIL ACTION NUMBER:

2:20-cv-13103-EP-LHG

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

Defendants.

BENCH TRIAL VOL. 7

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
December 8, 2022  
Commencing at 9:53 a.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
                         UNITED STATES DISTRICT JUDGE**

1 A. Yes, they do.

2 Q. So if I were to highlight the portion of the label that  
3 aligns with the asserted claims, what portion would that be?

4 A. Section 2.3.

5 Q. And even then, would it be all of Section 2.3, Dr. Berger?

6 A. No, only the portion that addresses four to nine months  
7 since last injection.

8 Q. The portion that's been blown up and is highlighted in  
9 green?

10 A. Yes, that's correct.

11 Q. Okay. So the portion that you've highlighted there,  
12 that's the portion that actually aligns with the claims; is  
13 that right?

14 A. Yes.

15 Q. Okay.

16 Now, do the Asserted Claims cover any other portion  
17 of the Trinza label?

18 A. No, they don't.

19 Q. Okay.

20 MR. MUKERJEE: Scott, if you could highlight the rest  
21 of the pages then, just in red.

22 BY MR. MUKERJEE:

23 Q. And so the indication of the medication itself is now in  
24 red.

25 Do you agree, Dr. Berger?

1 you?

2 A. It means doubt.

3 Q. It means a doubt?

4 A. Yes.

5 Q. Well, then, to that end, you've previously testified that  
6 it's unsafe to follow the missed dose regimen.

7 Do you recall that?

8 A. I do recall that.

9 Q. So would it be unsafe in all instances, Dr. Berger?

10 A. No, not in all instances.

11 Q. Could you further explain that?

12 A. Sure. So there are adherent patients and there are  
13 nonadherent patients. An adherent patient who is known to be  
14 adherent, I think that it is safe or wise or permissible to go  
15 ahead and use that reinitiation regimen in Claim 5 because the  
16 patient is likely to do those steps in the claim. Whereas with  
17 a nonadherent patient, a patient who's known to be nonadherent,  
18 he's unlikely to come back for the second reinitiation loading  
19 dose and unlikely to come back for the reinitiation dose of  
20 PP3M. So it's far safer -- and maybe wiser is a better word --  
21 it's far wiser to use a three-month injection for that  
22 nonadherent patient, cover the symptoms for three months, than  
23 to use a one-month injection that covers the symptoms for only  
24 one month.

25 Q. Thank you.



1 MR. MUKERJEE: Your Honor, you sustained the  
2 objection already.

3 THE COURT: Let's move on.

4 MR. FISCHER: Okay.

5 BY MR. FISCHER:

6 Q. Dr. Berger, all of your testimony today in your view is  
7 consistent with your testimony from last week?

8 A. Yes.

9 Q. Have you attempted to change or modify any of your  
10 testimony from last week today?

11 MR. MUKERJEE: Objection, Your Honor.

12 MR. FISCHER: I just want to know whether he did. If  
13 the answer is no, then we could move on.

14 MR. MUKERJEE: He's changed -- I don't even  
15 understand. He's changed it -- this is cross. If there's  
16 something he thinks he wants --

17 THE COURT: I think it's a fair question. He can ask  
18 that.

19 Go ahead.

20 A. I've clarified what I meant when I said unsafe. I  
21 clarified it to -- perhaps a better word would have been  
22 unwise.

23 BY MR. FISCHER:

24 Q. Dr. Berger, you said a couple times that you've been  
25 practicing for over 50 years at this point, correct?

1 with this.

2 So finish this off.

3 MR. FISCHER: Thank you, Your Honor. I just hope  
4 that if anyone looks into whether I fulfilled my promise to be  
5 short, we account for the length of the speaking objections.

6 BY MR. FISCHER:

7 Q. So the question, Dr. Berger, is in fact you had some  
8 reluctance to prescribe Trinza when it first came out, correct?

9 THE COURT: He already answered that question.

10 Move on.

11 BY MR. FISCHER:

12 Q. Your colleagues were similarly reluctant to prescribe  
13 Trinza when it first came out, right?

14 A. Not reluctant. No, I wasn't reluctant and my colleagues  
15 were not reluctant. We were -- we were questioning whether it  
16 would really last three months.

17 Q. Well, the question is: Did you have any reluctance to  
18 prescribe it when it came out?

19 A. Oh, that question. Sure.

20 It didn't stop me from prescribing it.

21 Q. Right. So now that Trinza has been around, you've  
22 concluded that it's indeed a wonderful drug, correct?

23 A. I thought it was a wonderful drug when it first came out.

24 And I still do.

25 Q. Thank you.

1 secondary considerations, of course. But with noninfringement,  
2 the way we tried this case to you, at least that was done, that  
3 was finished, right, plaintiffs' burden. It was finished and  
4 then we moved on to the invalidity segment.

5 MS. MULLIN: Your Honor, I agree that both parties in  
6 cross-examination have frankly had some difficulty trying to  
7 elicit testimony about things like long felt need and whether  
8 or not the missed dose instructions contributed to the success  
9 of the product. It's been hard to do that without coming close  
10 to what seems like infringement issues. That's just the nature  
11 of this case. So both parties have objected to using testimony  
12 elicited in the secondary considerations context for purposes  
13 of infringement. Okay? That's what happened yesterday and  
14 that was what was going on here today.

15 The issue that I'm talking about is quite different.  
16 Secondary considerations are directly related to obviousness,  
17 and Dr. Berger has confirmed today what Dr. Sommi said, that it  
18 would not be obvious for someone to give first a dose of PP1M  
19 to a patient that had missed a dose of PP3M. That's different.  
20 So we could agree we won't use it for infringement, but I think  
21 it's totally fair to game to use it for obviousness,  
22 particularly when the limits on cross-examination were based on  
23 testimony that was elicited on cross-examination.

24 What Dr. Berger said today was in response to his own  
25 counsel's questioning. I don't see any reason why we should be

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

JANSSEN PHARMACEUTICALS, INC.,  
JANSSEN PHARMACEUTICA NV,  
JANSSEN RESEARCH & DEVELOPMENT,  
LLC,

Plaintiffs,

vs.

CIVIL ACTION NUMBER:

2:20-cv-13103-EP-LHG

MYLAN LABORATORIES LIMITED,  
MYLAN PHARMACEUTICALS INC.,  
and MYLAN INSTITUTIONAL LLC,

Defendants.

BENCH TRIAL VOL. 8

MARTIN LUTHER KING BUILDING & U.S. COURTHOUSE  
50 Walnut Street  
Newark, New Jersey 07101  
December 9, 2022  
Commencing at 10:00 a.m.

**B E F O R E:        THE HONORABLE EVELYN PADIN,  
                         UNITED STATES DISTRICT JUDGE**

1 Sustenna patients that move over, that are switched over to  
2 Invega Trinza. I think this also confirms my understanding of  
3 the nexus here because we understand from Dr. Kohler that a key  
4 contributor to a physician's decision to switch a patient who  
5 is otherwise stable on Invega Sustenna to Invega Trinza is the  
6 confidence that's provided by the missed dosing instructions in  
7 the label, given the problem of nonadherence in this  
8 marketplace.

9 Q. You mentioned Dr. Kohler. He testified that he had only  
10 administered the four to nine month missed dose regimen to five  
11 of his patients.

12 Does your nexus analysis only apply to patients who  
13 received a dose pursuant to the regimen?

14 A. No, not at all. I mean, I think an important thing to  
15 remember here is there is value to having the option. All  
16 doctors know that nonadherence is a problem, so they need to  
17 have comfort that they know what to do and how do treat a  
18 patient who would be nonadherent. I think from an economic  
19 perspective what we say is there's an option value, the fact  
20 that a feature can have value even if it's not used.

21 Use is often a poor proxy for value. I think a great  
22 example is the airbag in an automobile. So I wouldn't buy a  
23 car without an airbag, even though I've never used one and I  
24 hope never to use one.

25 So I think use is often a poor proxy for value. The

1 important thing is the extent to which it affects the purchase  
2 decision.

3 Q. What is your overall conclusion regarding commercial  
4 success?

5 A. My overall conclusion is that Invega Trinza has been a  
6 success in the marketplace and the Asserted Claims of the '693  
7 patent have contributed to that success, so there is a nexus.

8 MR. QUIRK: No further questions at this time.

9 (CROSS-EXAMINATION)

10 MR. SODIKOFF: Good morning, Your Honor.

11 BY MR. SODIKOFF:

12 Q. Brian Sodikoff for Mylan.

13 Good morning, Ms. Mulhern.

14 I'd just like to ask you some questions about your  
15 testimony there. Just for the record, Trinza was approved in  
16 May of 2015 and then commercially launched in June of 2015.

17 Is that your understanding?

18 A. Yes, it is.

19 Q. You understand that here Janssen's asserting that Mylan  
20 infringes Claim 5 to 7 and 9 to 14 of the '693 patent, correct?

21 A. Yes, that's right.

22 Q. I think you said this in your opening -- or in your  
23 direct, but the Asserted Claims don't cover the active  
24 ingredient paliperidone palmitate molecule itself, right?

25 A. That's consistent with my understanding.

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS,  
INC., JANSSEN PHARMACEUTICA  
NV, and JANSSEN RESEARCH &  
DEVELOPMENT, LLC

Plaintiffs,

v.

MYLAN LABORATORIES LIMITED,

Defendant.

Civil Action No. 3:20-cv-13103-EP-  
LDW

(Consolidated)

*Document Electronically Filed*

**NOTICE OF APPEAL**

**NOTICE** is hereby given that Mylan Laboratories Limited, Defendant in the above-captioned case, hereby appeals to the United States Court of Appeals for the Federal Circuit from the final judgment entered on May 23, 2023 (Dkt. No. 174), and all other judgments, rulings, opinions, decisions, and orders merged therein. *See* Fed. R. App. P. 3(c)(4). This includes, but is not limited to, the District Court's findings of fact and conclusions of law entered on May 15, 2023. (Dkt. No. 171.)

Dated: May 26, 2023

Respectfully submitted,

**SAIBER LLC**

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**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

JANSSEN PHARMACEUTICALS,  
INC., JANSSEN PHARMACEUTICA  
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DEVELOPMENT, LLC

Plaintiffs,

v.

MYLAN LABORATORIES LIMITED,  
  
Defendant.

Civil Action No. 3:20-cv-13103-EP-  
LDW

(Consolidated)

**CERTIFICATE OF SERVICE**

*Document Electronically Filed*

**ARNOLD B. CALMANN** hereby certifies as follows:

I am an attorney-at-law of the State of New Jersey and a member of the firm of Saiber LLC, attorneys for Defendant Mylan Laboratories Limited (“Defendant”) in the above matter. I hereby certify that, on this 26th day of May, 2023, I caused a copy of Defendant’s Notice of Appeal and this Certificate of Service, to be served on counsel of record by CM/ECF and electronic mail.

/s Arnold B. Calmann  
ARNOLD B.CALMAN



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September 10, 2021

**VIA ECF**

Hon. Zahid N. Quraishi, U.S.D.J.  
Hon. Lois H. Goodman, U.S.M.J.  
Clarkson S. Fischer Building  
United States District Court  
District of New Jersey  
402 East State Street  
Trenton, New Jersey 08608

**Re: *Janssen Pharmaceuticals, Inc., et al. v. Mylan Laboratories Limited, et al.***  
**Civil Action No. 3:20-cv-13103 (ZNQ)(LHG)**

Dear Judge Quraishi and Magistrate Judge Goodman:

This Firm, along with Patterson Belknap Webb & Tyler, LLP, represents the Plaintiffs Janssen Pharmaceuticals, Inc., Janssen Pharmaceutica NV, and Janssen Research & Development, LLC, in the above-captioned matter. As the Court is aware, Paragraph 6 of the July 20, 2021 Joint Stipulation and Order Regarding Scheduling on (D.E. 38) required the parties to file a Joint Claim Construction and Pre-Hearing Statement by September 10, 2021. I am writing on behalf of all parties to advise Your Honor that the parties have determined that there are no claim terms that need to be construed in this lawsuit and that therefore there is no need for the parties to file a Joint Claim Construction and Pre-Hearing Statement or for the Court to schedule *Markman* briefing or a *Markman* hearing.<sup>1</sup>

We thank the Court for its kind consideration of this submission. Should Your Honor have any questions, we are available at the Court's convenience.

Respectfully,

s/ Keith J. Miller

---

<sup>1</sup> There are certain terms that MLL maintains are indefinite. MLL reserves its right to raise the indefiniteness arguments disclosed in MLL's Invalidity Contentions at trial. Janssen will not use the parties' agreement not to engage in *Markman* proceedings as a basis to object to MLL's raising at trial the indefiniteness defenses that are disclosed in MLL's Invalidity Contentions.

PTX-0001



US010143693B2

(12) **United States Patent**  
**Gopal et al.**(10) **Patent No.: US 10,143,693 B2**(45) **Date of Patent: Dec. 4, 2018**(54) **DOSING REGIMEN FOR MISSED DOSES  
FOR LONG-ACTING INJECTABLE  
PALIPERIDONE ESTERS**(58) **Field of Classification Search**

None

See application file for complete search history.

(71) Applicant: **JANSSEN PHARMACEUTICALS,  
INC.**, Titusville, NJ (US)(56) **References Cited**

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Osborne et al. "Health-related quality of life advantage of long-acting injectable and antipsychotic treatment for schizophrenia: a time trade-off study". *Health and Quality of Life Outcome*, pp. 1-9, 2012, 10:35.*Primary Examiner* — Bong-Sook Baek(57) **ABSTRACT**

The present application provides a method for treating patients in need of psychiatric treatment, wherein said patient is being treated with the 3-month formulation of paliperidone palmitate and fails to take the next scheduled dose of the 3-month formulation of paliperidone palmitate.

**29 Claims, 7 Drawing Sheets**(72) Inventors: **Srihari Gopal**, Belle Mead, NJ (US);  
**Paulien Gerarda Maria Ravenstijn**,  
Waalre (NL); **Alberto Russu**, Lange  
Nieuwstraat (BE); **Mahesh Narain  
Samtani**, Flemington, NJ (US)(73) Assignee: **Janssen Pharmaceuticals, Inc.**, Beerse  
(BE)(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.(21) Appl. No.: **15/090,889**(22) Filed: **Apr. 5, 2016**(65) **Prior Publication Data**

US 2017/0281629 A1 Oct. 5, 2017

**Related U.S. Application Data**(60) Provisional application No. 62/162,596, filed on May  
15, 2015, provisional application No. 62/144,054,  
filed on Apr. 7, 2015.(51) **Int. Cl.**  
**A61K 31/519** (2006.01)  
**A61K 9/00** (2006.01)  
**A61K 9/14** (2006.01)(52) **U.S. Cl.**  
CPC ..... **A61K 31/519** (2013.01); **A61K 9/0019**  
(2013.01)

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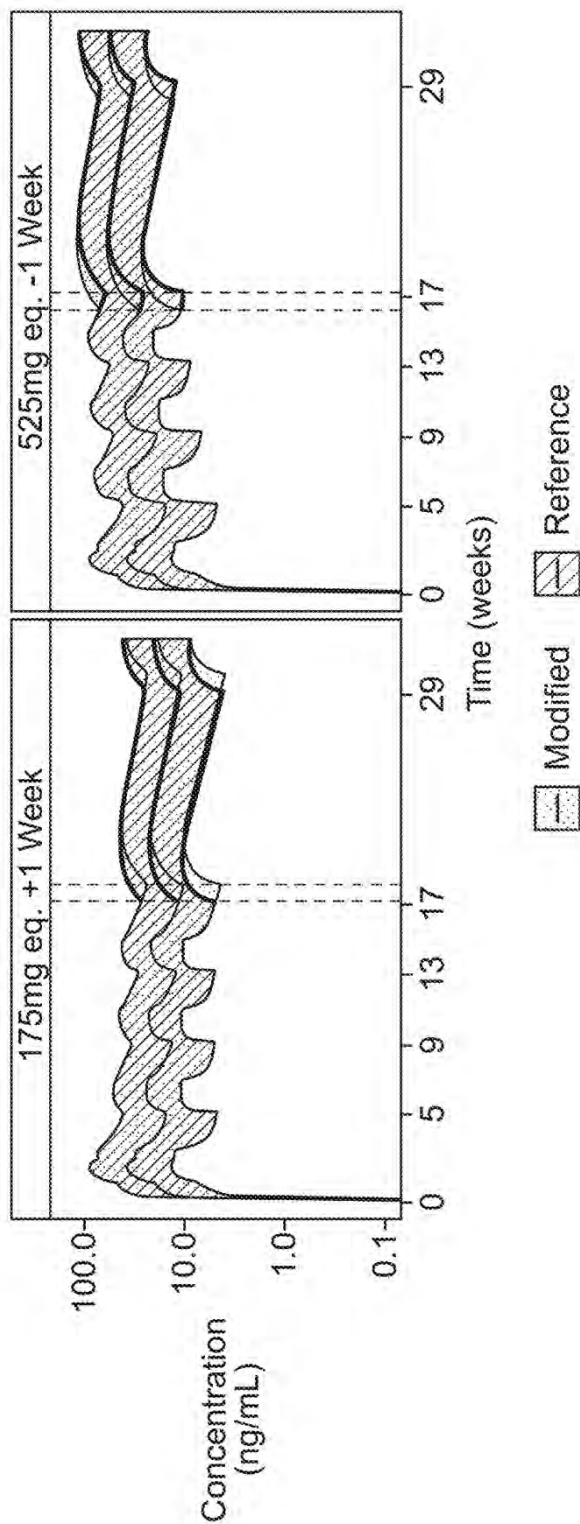
U.S. Patent

Dec. 4, 2018

Sheet 1 of 7

US 10,143,693 B2

**FIG. 1**



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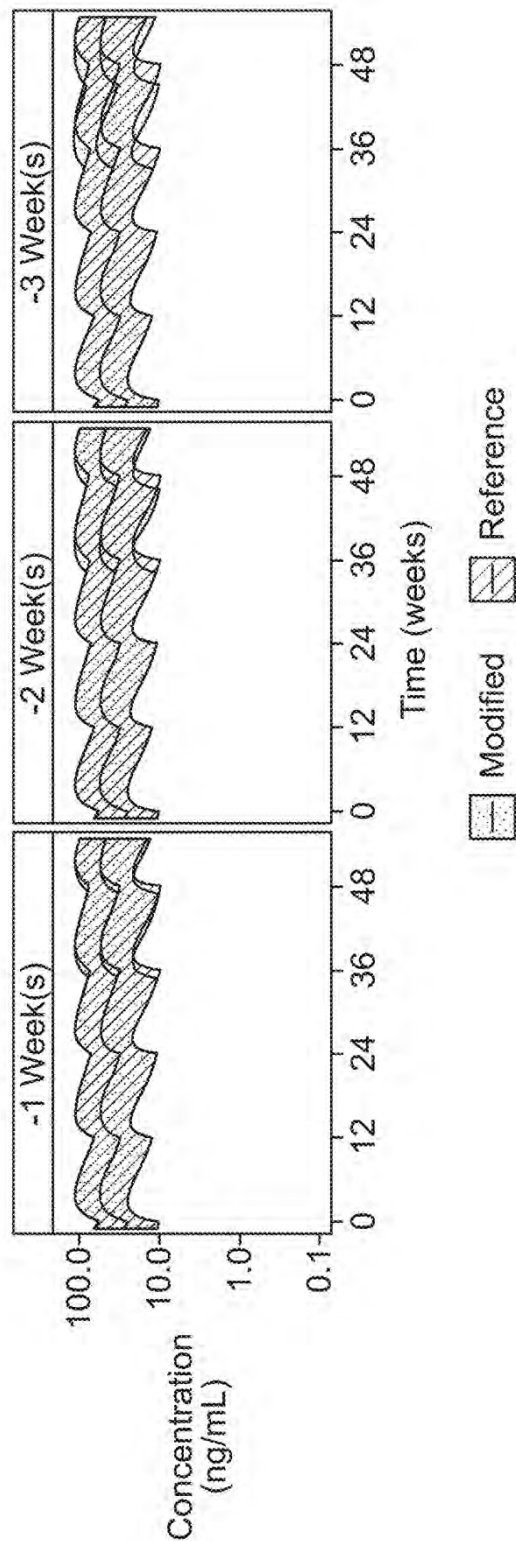
U.S. Patent

Dec. 4, 2018

Sheet 2 of 7

US 10,143,693 B2

**FIG. 2A**



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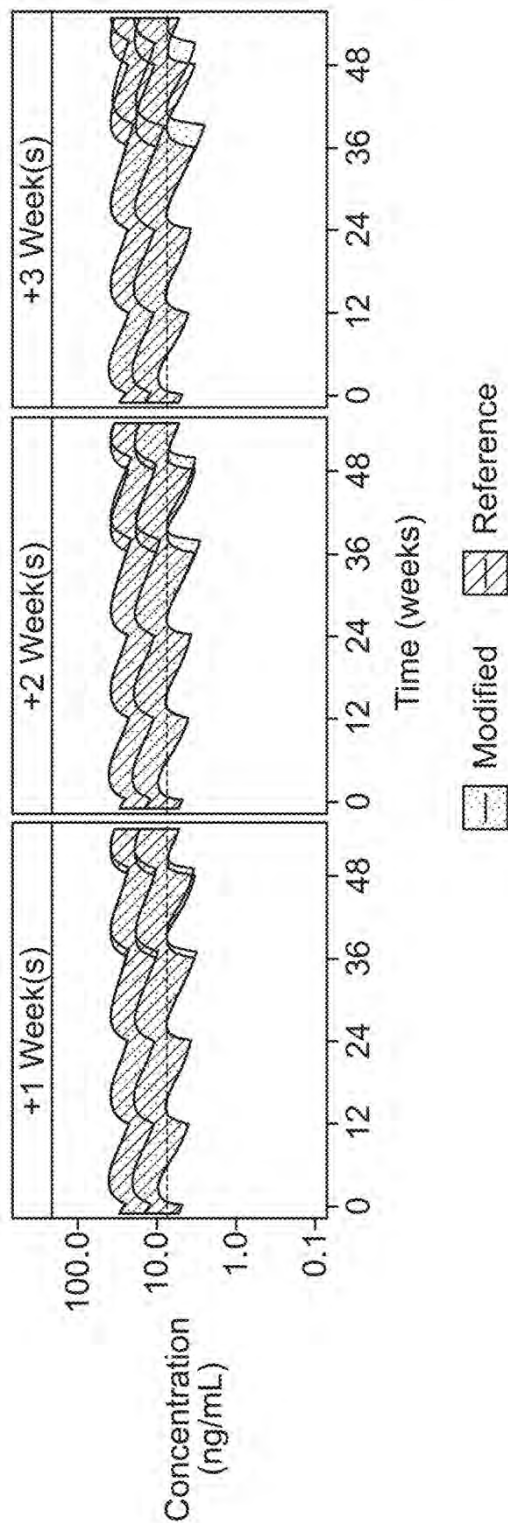
U.S. Patent

Dec. 4, 2018

Sheet 3 of 7

US 10,143,693 B2

**FIG. 2B**



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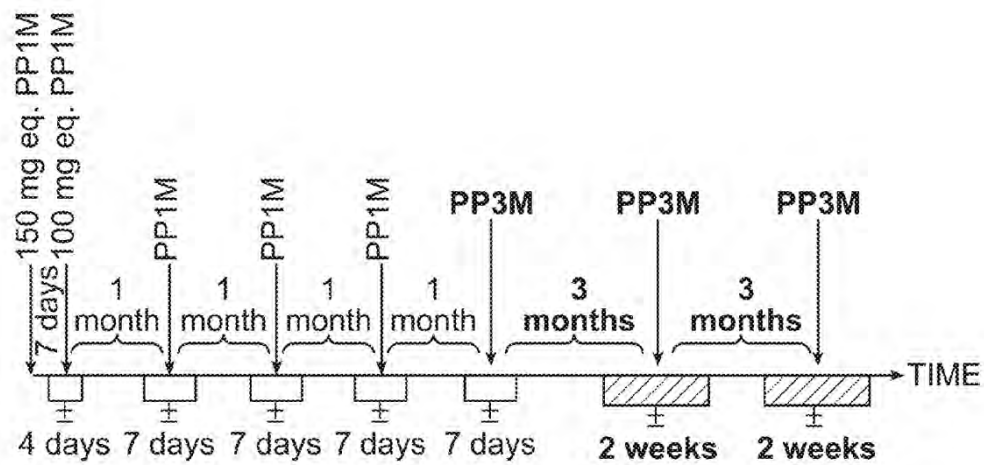
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Dec. 4, 2018

Sheet 4 of 7

US 10,143,693 B2

**FIG. 3**



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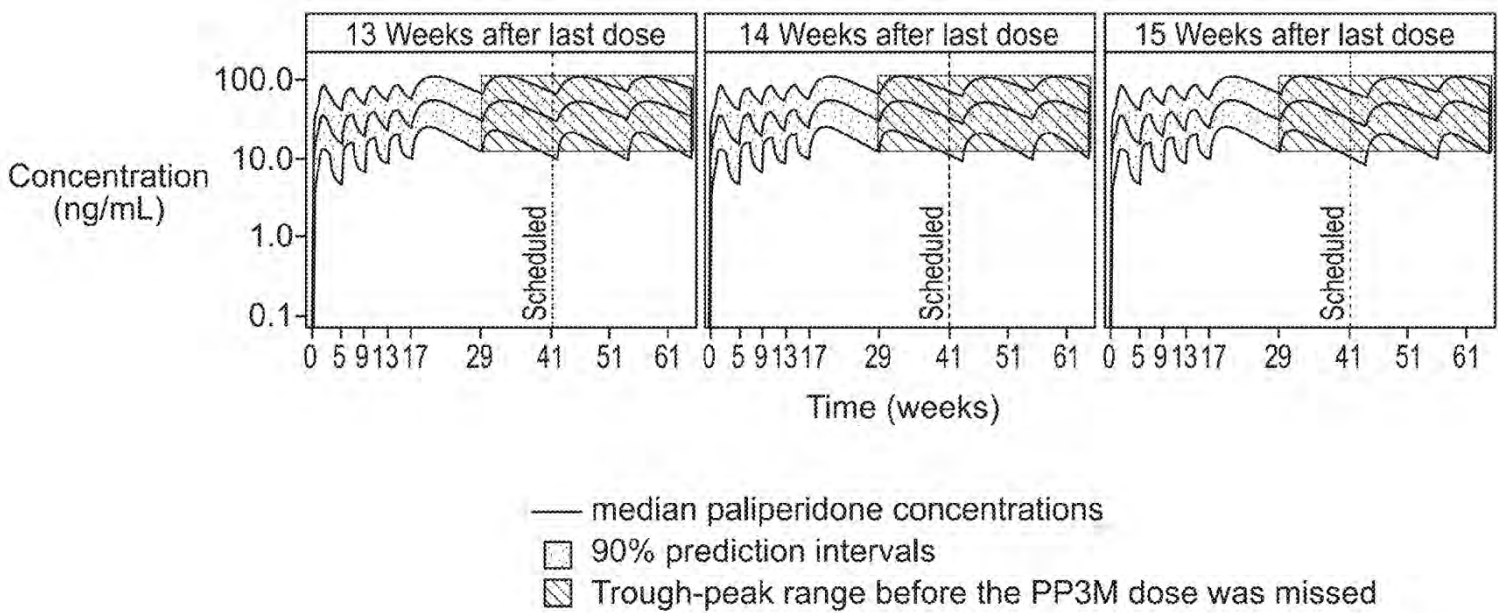
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Dec. 4, 2018

Sheet 5 of 7

US 10,143,693 B2

**FIG. 4A**



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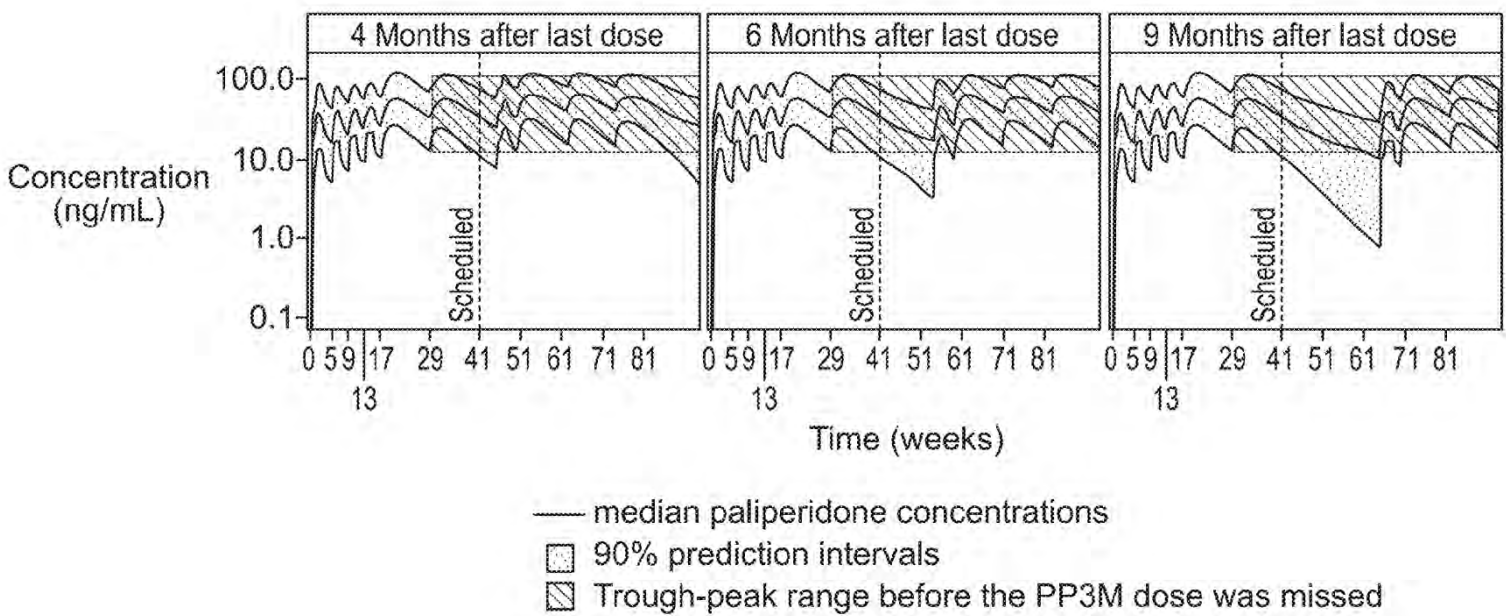
U.S. Patent

Dec. 4, 2018

Sheet 6 of 7

US 10,143,693 B2

**FIG. 4B**



Appx10006

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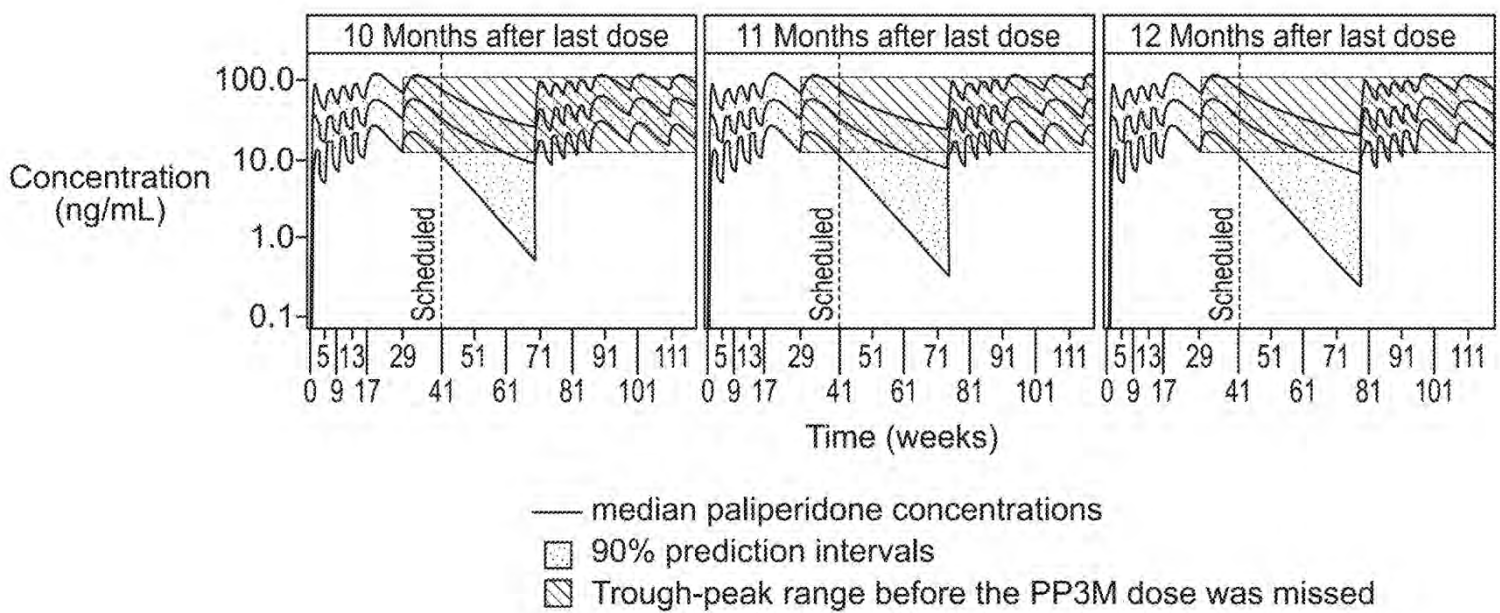
U.S. Patent

Dec. 4, 2018

Sheet 7 of 7

US 10,143,693 B2

**FIG. 4C**



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US 10,143,693 B2

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# **DOSING REGIMEN FOR MISSED DOSES FOR LONG-ACTING INJECTABLE PALIPERIDONE ESTERS**

## **CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims priority from U.S. Application No. 62/144,054, filed on Apr. 7, 2015 and Application No. 62/162,596, filed on May 15, 2015, each of which is incorporated herein by reference

## **FIELD OF THE INVENTION**

This invention relates to a method for treating patients who have missed a treatment of 3-month paliperidone palmitate extended-release injectable suspension formulation.

## **BACKGROUND OF THE INVENTION**

Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Antipsychotics were first introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D<sub>2</sub> and serotonin (5-hydroxytryptamine type 2A) antagonism of the second generation, atypical antipsychotic drugs. Paliperidone (9-OH risperidone) is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

3-monthly Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other related diseases that are normally treated with antipsychotic medications. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

Many patients with the mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. adherence problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies. Once monthly Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone, which may greatly enhance compliance with dosing. Paliperidone palmitate formulated as an aqueous nanosuspension is described in U.S. Pat. Nos. 6,077,843 and 6,555,544. In addition, a dosing regimen of paliperidone palmitate for treating patients is disclosed in US Patent Application Publication No. 20090163519.

2

Paliperidone palmitate is an atypical antipsychotic drug administered by injection. The original formulation of paliperidone palmitate was a once-monthly antipsychotic and was approved for the treatment of schizophrenia in adults in numerous countries. The acute and sustained efficacy and tolerability profile of once-monthly paliperidone palmitate has been demonstrated in clinical studies totalling more than 3800 patients. Continued treatment with once-monthly paliperidone palmitate in patients who initially responded to it for acute worsening of symptoms resulted in a nearly 4-fold reduction in relapse risk compared with patients randomized to placebo. A recently developed 3-month formulation offers a substantially longer dosing interval: injections are administered once every 3 months. This extended dosing interval offers the prospect of fewer opportunities for nonadherence than currently available long acting injectable formulations, thus reducing relapse risk as a result of subtherapeutic plasma concentration and its associated negative consequences in patients with schizophrenia.

Even with a drug administered once every 3 months or every 12 weeks ( $\pm 3$  weeks) or 13 weeks  $\pm 2$ , patients at time miss their doses of medication. Consequently, there is a need to reinstitute a dosing regimen for patients who miss their regularly scheduled dose of medication. Thus, the objective of the present application is to provide a dosing regimen of paliperidone palmitate for patients in need of a treatment who have missed their 3 month ( $\pm 2$  weeks) dose of paliperidone palmitate 3-month extended-release injectable suspension.

## **SUMMARY OF THE INVENTION**

In one embodiment of the present invention there is provided a dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with a 3-month injectable paliperidone palmitate depot, wherein said patient misses for a period of between about four months and about nine months (inclusive e.g. four months or more but nine months or less) the next scheduled maintenance dose of the 3-month injectable paliperidone palmitate depot, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of the monthly injectable paliperidone palmitate depot on day one;
- (2) administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation dose of the monthly injectable paliperidone palmitate depot on about the 8<sup>th</sup> day  $\pm 4$  (e.g. 4th day to about the 12th day) after administering of said first reinitiation loading dose; and

Missed PP3M dose	Administer PP1M, two doses (into deltoid muscle)		Then administer PP3M (into deltoid <sup>a</sup> or gluteal muscle) Maintenance Dose
	First Reinitiation Dose	Second Reinitiation Dose	
175 mg eq.	50 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	100 mg eq.	525 mg eq.

- (3) administer intramuscularly in the deltoid or gluteal muscle of said patient the 3-month formulation of

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US 10,143,693 B2

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paliperidone palmitate in the range of about 175 mg eq. to about 525 mg eq. on about the 30th day $\pm$ 7 (e.g. 23rd day to about the 37th day) after administering of the second reinitiation dose of monthly injectable paliperidone palmitate.

In another embodiment of the present invention there is provided a dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with a 3-month injectable paliperidone palmitate depot, wherein said patient misses for a period of more than nine months the next scheduled maintenance dose of the 3-month injectable paliperidone palmitate depot, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of 150 mg eq. of the monthly injectable paliperidone palmitate depot;
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of 100 mg eq. the monthly injectable paliperidone palmitate depot on about the 4th day to about the 12th day after administering of said first reinitiation loading dose;
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a first reinitiation maintenance dose of 50 mg eq. to about 150 mg eq. of the monthly injectable paliperidone palmitate depot on about the 23th day to about the 37th day after administering of said second reinitiation loading dose;
- (4) administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of monthly injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of the first maintenance additional dose;
- (5) administering intramuscularly in the deltoid or gluteal muscle of said patient a third reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of monthly injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of the second maintenance dose; and
- (6) administering intramuscularly in the deltoid or gluteal muscle of said patient from about 175 mg eq. to about 525 mg eq. of the 3-month formulation of paliperidone palmitate on about the 23rd day to about the 37th day after administering of the third maintenance dose of monthly injectable paliperidone palmitate.

Additional maintenance doses may be administered before the readministration of the 3-month formulation of paliperidone palmitate (e.g. a fourth maintenance dose, fifth maintenance dose).

This and other objects and advantages of the present invention may be appreciated from a review of the present application.

#### DETAILED DESCRIPTION OF FIGURES

FIG. 1 illustrates the switching from PP1M to PP3M at default week 17 $\pm$ 1 Week.

FIGS. 2A-2B illustrate the dosing windows around the regularly scheduled 12-week dosing interval. Graphs of modeled results of dosing before regularly scheduled injections of (A) 525 mg eq. PP3M (B) 175 mg eq. PP3M.

FIG. 3 illustrates the dosing windows for PP1M and PP3M dosing regimen.

4

FIGS. 4A-4C illustrate predicted plasma concentration of PP3M (525 mg eq.). Graphs of modeled results of missed dosing for (A) <4 months. (B) between 4 to 9 months (C) >9 months.

#### DETAILED DESCRIPTION

3-month paliperidone palmitate extended-release injectable suspension is an antipsychotic medication which is the ester of the active ingredient paliperidone. Paliperidone is effective for the treatment of psychosis and has been used to treat schizophrenia and schizoaffective disorders. The 3-month paliperidone palmitate extended-release injectable suspension suitable for the treatment of psychotic disorders including but not limited to schizophrenia and/or schizoaffective disorders. It is recommended that the 3-month paliperidone palmitate extended-release injectable suspension be administered to patients who have been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension (e.g. INVEGA SUSTENNA®) for a several months and it is recommended for at least four months.

3-month paliperidone palmitate extended-release injectable suspension preferably will be provided with an adequate dose of paliperidone palmitate generally in the range of about 250 mg to about 900 mg of paliperidone palmitate to provide a sustained therapeutic concentration of paliperidone over the three month dosing interval to the patient. Preferably the aqueous extended-release suspension for intramuscular injection will be provided in dose strengths of about 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate. The drug product hydrolyzes to the active moiety, paliperidone, resulting in dose strengths of 175 mg eq., 263 mg eq., 350 mg eq., and 525 mg eq. of paliperidone, respectively. 3-month paliperidone palmitate extended-release injectable suspension is preferably provided in a prefilled syringe (cyclic-olefin-copolymer) prefilled with either 175 mg eq. (0.875 mL), 263 mg eq. (1.315 mL), 350 mg eq. (1.75 mL), or 525 mg eq. (2.625 mL) paliperidone (as 273 mg, 410 mg, 546 mg, or 819 mg paliperidone palmitate) suspension with a plunger stopper and tip cap (bromobutyl rubber), a backstop, and 2 types of commercially available needles: a thin walled 22G, 1½-inch safety needle and a thin walled 22G, 1-inch safety needle.

3-month paliperidone palmitate extended-release injectable suspension is intended for intramuscular use only. It is not recommended not to administer by any other route. Care should be taken to avoid inadvertent injection into a blood vessel. Dose should be administered in a single injection; it should not be administered in divided injections as this would change the release profile and has not been studied in clinical trials. It is preferred that injections be administered slowly, deep into the deltoid or gluteal muscle. 3-month paliperidone palmitate extended-release injectable suspension is preferred to be administered using only the thin wall needles to reduce the risk of blockage.

#### Deltoid Injection

Currently the recommended needle size for administration of 3-month paliperidone palmitate extended-release injectable suspension into the deltoid muscle is determined by the patient's weight:

For patients weighing less than 90 kg, the 1-inch, 22 gauge thin wall needle is recommended.

For patients weighing 90 kg or more, the 1½-inch, 22 gauge thin wall needle is recommended.

It is currently preferred that 3-month paliperidone palmitate extended-release injectable suspension be administered into the center of the deltoid muscle. It is also preferred that deltoid injections should be alternated between the two deltoid muscles.

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US 10,143,693 B2

5

**Gluteal Injection**

Currently, the preferred needle size for administration of 3-month paliperidone palmitate extended-release injectable suspension into the gluteal muscle is the 1½-inch, 22 gauge thin wall needle regardless of patient weight. It is preferred that 3-month paliperidone palmitate extended-release injectable suspension be administered into the upper-outer quadrant of the gluteal muscle. It is also preferred that gluteal injections should be alternated between the two gluteal muscles.

**Incomplete Administration**

To avoid an incomplete administration of 3-month paliperidone palmitate extended-release injectable suspension, it is recommended that to ensure that doses are completely administered that the syringes be vigorously shaken and/or mechanical agitated to obtain a uniform dispersion of the suspension, preferably the suspension will be shaken vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension and ensure the needle does not get clogged during injection.

It is preferred that 3-month paliperidone palmitate extended-release injectable suspension is to be used only after the 1-month paliperidone palmitate extended-release injectable suspension (e.g. INVEGA SUSTENNA®) has been established as adequate treatment for at least four months. In order to establish a consistent maintenance dose, it is preferred that at least the last two doses of 1-month paliperidone palmitate extended-release injectable suspension be the same dosage strength before starting 3-month paliperidone palmitate extended-release injectable suspension.

The preferred time to initiate dosing a patient with 3-month paliperidone palmitate extended-release injectable suspension is when the next 1-month paliperidone palmitate dose was to be scheduled with a 3-month paliperidone palmitate extended-release injectable suspension dose based on the previous 1-month injection dose as shown in Table 1. 3-month paliperidone palmitate extended-release injectable suspension may be administered up to about 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.

TABLE 1

Conversion From the Last 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension (INVEGA SUSTENNA®) Dose To the 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension (INVEGA TRINZA™) Dose Using 3.5 as a Multiplier	
If the last 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension dose is about:	Initiate 3-month paliperidone palmitate extended-release injectable suspension at about the following dose:
50 mg eq.	175 mg eq.
75 mg eq.	263 mg eq.
100 mg eq.	350 mg eq.
150 mg eq.	525 mg eq.

Conversion from the 39 mg 1-month paliperidone palmitate extended-release injectable suspension was not studied.

Following the initial 3-month paliperidone palmitate extended-release injectable suspension, 3-month paliperidone palmitate extended-release injectable suspension

6

should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 273 mg to 819 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of 3-month paliperidone palmitate extended-release injectable suspension, the patient's response to an adjusted dose may not be apparent for several months.

**Missed Doses****Dosing Window**

Missing doses of 3-month paliperidone palmitate extended-release injectable suspension should be avoided. However, on exceptional occasions, patients may be given the injection up to about 2 weeks before or after the 3-month time point.

**Missed Dose >3½ Months and <4 Months Since Last Injection**

If more than 3½ months (up to but less than 4 months) have elapsed since the last injection of 3-month paliperidone palmitate extended-release injectable suspension, the previously administered 3-month paliperidone palmitate extended-release injectable suspension dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

**Missed Dose Greater than or Equal to 4 Months Up to 9 Months Since Last Injection**

If between 4 to 9 months have elapsed since the last injection of 3-month paliperidone palmitate extended-release injectable suspension, do NOT administer the next dose of 3-month paliperidone palmitate extended-release injectable suspension. Instead, use the re-initiation regimen shown in Table 2.

TABLE 2

Re-Initiation Regimen After Missing ≥4 months up to 9 Months of 3-Month Extended-Release Injectable Suspension Dose				
Last 3-Month Extended-Release Injectable Suspension	Administer PP1M, two doses one week apart (into deltoid muscle)		Then administer 3-Month Extended-Release Injectable Suspension	Dose (into deltoid <sup>a</sup> or gluteal muscle)
dose	Day 1	Day 8	1 month after day 8	
175 mg eq.	50 mg eq.	→ 50 mg eq.	→ 175 mg eq.	
263 mg eq.	75 mg eq.	→ 75 mg eq.	→ 263 mg eq.	
350 mg eq.	100 mg eq.	→ 100 mg eq.	→ 350 mg eq.	
525 mg eq.	100 mg eq.	→ 100 mg eq.	→ 525 mg eq.	

<sup>a</sup>See Instructions for Use for deltoid injection needle selection based on body weight.

**Missed Dose >9 Months Since Last Injection**

If more than 9 months have elapsed since the last injection of 3-month paliperidone palmitate extended-release injectable suspension, re-initiate treatment with the 1-month paliperidone palmitate extended-release injectable suspension as described in the prescribing information for that product. 3-month paliperidone palmitate extended-release injectable suspension can then be resumed after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least 4 months. 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension Dosing

The published US drug label for INVEGA SUSTENNA® 1-month paliperidone palmitate extended-release injectable suspension provides the appropriate dosing instructions for such product at various doses. This dosing regimen is also generally described in U.S. Patent Application No.

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US 10,143,693 B2

7

20090163519 for treating a psychiatric patient using paliperidone as a paliperidone palmitate ester in 1-month sustained release formulation. To attain a therapeutic plasma level of paliperidone, patients are administered to receive a first dose of paliperidone palmitate on day 1 of treatment, followed by a second dose between days 4 to 12 (and preferably about day 6 to 10) of treatment, then a third dose between days 29 to about 43 (and preferably from about 33 to about 39) of starting treatment. It is preferred that the patients will be administered the first dose on day 1, the second dose on day 8 after the first dose and the third dose on day 36 of after the first dose. The first two doses should be injected in the deltoid muscle. Thereafter paliperidone palmitate may be administered by injection approximately once a month (e.g. once every four weeks). To assure a potential therapeutic plasma level of paliperidone is attained, at least the first loading dose of about 150 mg-eq. of paliperidone as a paliperidone palmitate ester may be administered on day 1 of treatment. To further assure a potential therapeutic plasma level of paliperidone is attained by the patient, the first loading dose and the second loading dose ranging between from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate ester may be administered. To maintain a therapeutic level in the plasma, the subsequent doses thereafter or the maintenance dose ranging from about 25 mg-eq. to 150 mg-eq. per month may be administered. The maintenance dose may be administered intramuscularly into the deltoid or gluteal muscle, and the gluteal muscle is preferred. Those of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patients' conditions such as response to the medication and renal function.

The models have indicated that there may be flexibility in the duration of the second loading dose and the maintenance dose of the maintenance dosing regimen for the 1-month paliperidone palmitate extended-release injectable suspension. For example, the second loading dose may be administered within the duration of about the 8<sup>th</sup> day $\pm$ 4 days (or about 1 week $\pm$ 4 days) after administering of the first loading dose. Therefore, the second loading dose may be administered from about the 4<sup>th</sup> to about the 12<sup>th</sup> day after the first loading dose of the initial dosing. Similarly, the maintenance dose may be administered within the duration of about the 30<sup>th</sup> day $\pm$ 7 days after administering of the first loading dose. Therefore, the maintenance dose may be administered from about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day after administering of the second loading dose of the initial dosing. The flexible administration timing provides additional treatment benefit for patients who may require earlier administration or have missed their dose, within a short window, of the scheduled treatment without affecting the treatment effectiveness.

The models or simulations also indicate that 1-month paliperidone palmitate extended-release injectable suspension may be administered by intramuscular injection into either deltoid or gluteal muscle. The first and second loading dose of the initiation regimen may be administered in the deltoid muscle and the maintenance dose of the maintenance regimen may be administered in either the deltoid or gluteal muscle. The injection into the deltoid muscle may be delivered by a 1-inch 23-Gauge (G) or 1.5-inch 22-G needle based on the patient's weight. For the patients whose body weights are less than about 90 kg or 200 lb, a 1-inch 23-G needle may be used for administration, and for those body weights are equal or more than about 90 kg or 200 lb, a 1.5-inch 22-G needle may be used for administration. The injection into the gluteal muscle may be delivered by a 1.5-inch 22-G needle for all body weights.

8

By way of example, a dosing regimen is provided to switch patients from other injectable antipsychotic drug to 1-month paliperidone palmitate extended-release injectable suspension comprising administering into the deltoid muscle the initial dosing regimen comprising a first loading dose of about 234 mg of paliperidone palmitate and administering into the deltoid or gluteal muscle the maintenance regimen comprising a monthly maintenance dose of about 39 to about 234 mg of paliperidone palmitate on about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day after administering of the first loading dose.

For patients who have previously received oral antipsychotic drugs, a switching treatment to 1-month paliperidone palmitate extended-release injectable suspension may comprise an initial dosing regimen and a monthly dosing regimen. The initial dosing regimen may comprise administering a first loading dose of 1-month paliperidone palmitate and administering a second loading dose of 1-month paliperidone palmitate, and the maintenance dosing regimen may comprise administering a maintenance dose of 1-month paliperidone palmitate. The previous oral antipsychotics may be discontinued at the time of initiation of the switching treatment or administration of the first loading dosing of 1-month paliperidone palmitate.

The monthly maintenance dose may be determined based on the condition of the patient and/or the severity of the disease. The preferred first loading dose may range from about 156 mg to about 234 mg of paliperidone palmitate, and more preferably about 234 mg. The preferred second loading dose may range from about 78 mg to about 156 mg, and more preferably about 156 mg. The preferred monthly maintenance dose may range from about 39 to about 234 mg, and more preferably about 117 mg. Subsequently, based on the patient tolerability and/or the drug efficacy, the maintenance dose may be further adjusted monthly to achieve optimal treatment effectiveness. The patients may be monitored for several months to ensure the full effect of the dose adjustment because of the prolonged-release characteristic of paliperidone palmitate.

Based on the pharmacokinetic simulations, patients previously stabilized on paliperidone in oral tablets may attain similar paliperidone steady-state exposure during maintenance treatment with paliperidone palmitate intramuscular injection monthly. For example, patients stabilized on oral paliperidone of about 3 mg may attain similar paliperidone steady-state exposure with the intramuscular injection of paliperidone palmitate of about 39 mg to about 78 mg. Similarly, patients stabilized on oral paliperidone of about 6 mg and about 12 mg may attain similar paliperidone steady-state exposure with the intramuscular injection of paliperidone palmitate of about 117 mg and about 234 mg, respectively. Therefore, during the maintenance regimen, the patients previously stabilized on paliperidone in oral tablets may be administered with the appropriate dose of paliperidone palmitate in injectable formulation corresponding to the stabilized dose of oral paliperidone.

As used herein, the term "stabilized dose" refers to the dose which is to be administered according to the established dosing regimen. Preferably, the stabilized dose may be the maintenance dose of the monthly maintenance dosing regimen prior to a missed dose.

Also used herein, the terms "the first loading dose of the reinitiation regimen", "the first dose of the reinitiation regimen", "the first reinitiation dose" or variant thereof refer to the dose to be administered on day 1 when patients return to treatment. Similarly, the terms "the second loading dose of the reinitiation regimen", "the second dose of the reini-

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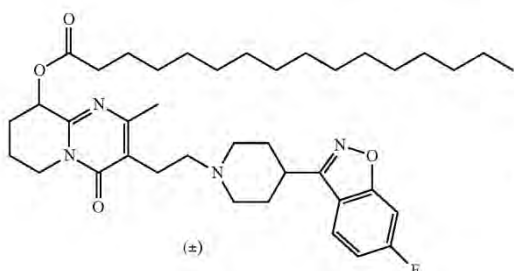
US 10,143,693 B2

9

tiation regimen", "the second reinitiation dose" or variant thereof refer to the dose to be administered after a week after the treatment day 1; and the terms "the maintenance dose of the reinitiation regimen", "the reinitiation maintenance dose" or variant thereof refer to the dose to be administered monthly after the treatment day 8.

#### Extended-Release Injectable Suspension Formulations

Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, which contains a racemic mixture of (+)- and (-)-paliperidone, which are described in U.S. Pat. No. 5,254,556 (incorporated herein by reference). The chemical name for paliperidone palmitate is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-c]pyrimidin-9-yl hexadecanoate. The structural formula is:



Paliperidone esters may be formulated with pharmaceutical excipients into injectable dosage forms as described in U.S. Pat. Nos. 5,254,556 and 6,077,843 both of which are incorporated herein by reference. Injectable formulations may be formulated in aqueous carriers.

Suitable aqueous depot formulations are described in U.S. Pat. No. 6,077,843 which is incorporated herein by reference. The 3-month formulations would have an average size of less than about 20  $\mu\text{m}$  to about 3  $\mu\text{m}$ . Preferably the particles would have an average particle size ( $d_{50}$ ) of from about 10  $\mu\text{m}$  to about 3  $\mu\text{m}$ ; preferably about 9  $\mu\text{m}$  to about 4  $\mu\text{m}$ .

The 1-month aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would be of an average size of less than about 2,000 nm to about 100 nm. Preferably the nano particles would have an average particle size ( $d_{50}$ ) of from about 1,600 nm to about 400 nm and most preferably about 1,400 nm to about 900 nm. Preferably the  $d_{90}$  will be less than about 5,000 nm and more preferably less than about 4,400 nm.

As used herein, an effective average particle size ( $d_{50}$ ) of less than about 2,000 nm means that at least 50% of the particles have a diameter of less than about 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least about 90%, e.g. about 5,000 nm. Most preferably, about 90% of the particles have a size of less than about 4,400 nm.

Suitable aqueous nanoparticle depot 1-month formulations are described in U.S. Pat. No. 6,555,544 which is incorporated herein by reference. In one embodiment of the present invention the formulation would comprise nanoparticles, a surfactant, a suspending agent, and optionally one or more additional ingredients selected from the group consisting of preservatives, buffers and an isotonicizing agent.

10

Useful surface modifiers paliperidone palmitate formulations are believed to include those that physically adhere to the surface of the active agent but do not chemically bond thereto. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available TWEENS<sup>TM</sup>, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecyl sulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminate silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as PLURONIC<sup>TM</sup> F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as TETRONIC<sup>TM</sup> 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT<sup>TM</sup> (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; DUPO-NOL<sup>TM</sup> P which is a sodium lauryl sulfate available from DuPont; TRITON<sup>TM</sup> X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; TWEEN<sup>TM</sup> 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Speciality Chemicals; SPAN<sup>TM</sup> 20, 40, 60 and 80 which are sorbitan esters of fatty acids; ARLACEL<sup>TM</sup> 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; CARBOWAX<sup>TM</sup> 3550 and 934 which are polyethylene glycols available from Union Carbide; CRODESTA<sup>TM</sup> F110 which is a mixture of sucrose stearate and sucrose distearate available from Croda Inc.; CRODESTA<sup>TM</sup> SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is  $\text{C}_{18}\text{H}_{17}\text{CH}_2(\text{CON}(\text{CH}_3)\text{CH}_2(\text{CHOH})_4\text{CH}_2\text{OH})_2$ . The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic<sup>TM</sup> F108 and Pluronic<sup>TM</sup> F68.

Pluronic<sup>TM</sup> F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula  $\text{HO}[\text{CH}_2\text{CH}_2\text{O}]_x[\text{CH}(\text{CH}_3)\text{CH}_2\text{O}]_y[\text{CH}_2\text{CH}_2\text{O}]_z\text{H}$  in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag NONIONIC<sup>TM</sup> 1108-F available from Hodag, and SYNPERONIC<sup>TM</sup> PE/F108 available from ICI Americas.

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US 10,143,693 B2

11

The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the antipsychotic agent, etc. The specific surface modifier preferably is present in an amount of about 0.1 to about 1 mg per square meter surface area of the paliperidone palmitate. It is preferred in the case of paliperidone palmitate (9-hydroxyrisperidone palmitate) to use PLURONIC™ F108 as a surface modifier, a relative amount (w/w) of both ingredients of approximately 6:1 is preferred.

The particles of this invention can be prepared by a method comprising the steps of dispersing paliperidone palmitate in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the antipsychotic agent to an effective average particle size. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

A general procedure for preparing the particles for the 1-month formulation described herein includes (a) obtaining paliperidone palmitate in micronized form; (b) adding the micronized paliperidone palmitate to a liquid medium to form a premix; and (c) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the effective average particle size.

The paliperidone palmitate in micronized form may be prepared using techniques known in the art. It is preferred that the particle size of the micronized paliperidone palmitate be less than about 100  $\mu\text{m}$  as determined by sieve analysis. If the particle size of the micronized paliperidone palmitate is greater than about 100  $\mu\text{m}$ , then it is preferred that the particles of paliperidone palmitate be reduced in size to less than 100  $\mu\text{m}$ .

The micronized paliperidone palmitate can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of paliperidone palmitate in the liquid medium (weight by weight percentage) can vary widely and depends on the selected antipsychotic agent, the selected surface modifier and other factors. Suitable concentrations of paliperidone palmitate in compositions vary from about 0.1% to about 60%, preferably is from about 0.5% to about 30%, and more preferably, is approximately 7% (w/v). It is currently preferred to use a concentration of about 100 mg eq of paliperidone per ml or about 156 mg of paliperidone palmitate per ml.

A more preferred procedure involves the addition of a surface modifier to the premix prior to its subjection to mechanical means to reduce the effective average particle size. The concentration of the surface modifier (weight by weight percentage) can vary from about 0.1% to about 90%, preferably from about 0.5% to about 80%, and more preferably is approximately 7% (w/v).

The premix can be used directly by subjecting it to mechanical means to reduce the effective average particle size in the dispersion to less than about 2,000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the antipsychotic agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation such as, for example, a roller mill or a Cowles type mixer, until a homogeneous dispersion is achieved.

The mechanical means applied to reduce the effective average particle size of the antipsychotic conveniently can

12

take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills—such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is anywhere between about 0.1 Pa·s and about 1 Pa·s. For ball milling, the apparent viscosity of the premix preferably is anywhere between about 1 mPa·s and about 100 mPa·s.

The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, about 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles which are acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and about 95% ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than about 2.5 g/cm<sup>3</sup> and include about 95% ZrO stabilized with magnesia and polymeric beads.

The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For rolling mills, processing times of up to two days or longer may be required for smaller size particles.

The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than about 30° C. to about 40° C. are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed by, for example, shaking vigorously. Optionally, the dispersion can be subjected to a sonication step using, for example, an ultrasonic power supply.

Aqueous compositions according to the present invention conveniently further comprise a suspending agent and a buffer, and optionally one or more of a preservative and an isotonicizing agent. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonicizing agent.

Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxy-propylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of about 0.5 to about 2%, most preferably about 1% (w/v).

Suitable wetting agents preferred from the listed surfactant for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a con-

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US 10,143,693 B2

13

centration of about 0.5% to about 3%, more preferably about 0.5% to about 2%, most preferably about 1.1% (w/v).

Suitable buffering agents are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to the pH value of about 8.5), preferably in the pH range of about 7 to about 7.5. Particularly preferred is the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9% (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6% (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein.

Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic acid, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-gamma-piccolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to about 2% (w/v), preferably up to about 1.5% (w/v).

Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from about 0% to about 10% (w/v) isotonizing agent. Mannitol may be used in a concentration from about 0% to about 7% more preferably, however, from about 1% to about 3% (w/v), especially from about 1.5% to about 2% (w/v) of one or more electrolytes are used to render the suspension isotonic, apparently because ions help to prevent flocculation of the suspended ester. In particular, electrolytes of the buffer serve as isotonizing agent.

A particularly desirable feature for an injectable depot formulation relates to the ease with which it can be administered. In particular such an injection should be feasible using a needle as fine as possible in a span of time which is as short as possible. This can be accomplished with the aqueous suspensions of the present invention by keeping the viscosity below about 75 mPa.s, preferably below about 60 mPa.s. Aqueous suspensions of such viscosity or lower can both easily be taken up in a syringe (e.g. from a vial), and injected through a fine needle (e.g. a 21G 1½ inch, 22G 2 inch, 22G 1¼ inch or 23G 1 inch needle). The preferred needles for injection are 22G 22G 1½ inch regular wall and 23G 1 inch regular wall needles.

Ideally, aqueous suspensions according to the present invention will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular for the 3-month formulation the composition will be (a) from about 280 to about 350 mg/mL of prodrug; (b) from about 8 to about 12 mg/mL of wetting agent; (c) from about 16 to about 22 mg/mL of one or more buffering agents to render the neutral to very slightly basic (pH 8.5); (d) from about 65 to about 85 mg/mL of a suspending agent; (e) up to about 2% (w/v) preservatives; and (f) water q.s. ad 100%. Most preferably the inactive ingredients in the 3-month formulation will be polysorbate 20 (about 10 mg/mL), polyethylene glycol 4000 (about 75 mg/mL), citric acid monohydrate (about 7.5 mg/mL), sodium dihydrogen phosphate monohydrate (about 6 mg/mL), sodium hydroxide (about 5.4 mg/mL) and water for injection. In particular, such a composition for the 1-month formulation will comprise by weight based on the total volume of the composition: (a) from about 3% to 20% (w/v) of the prodrug; (b) from about 0.5% to 2% (w/v) of a wetting agent; (c) one or more buffering agents sufficient to render the composition neutral

14

to very slightly basic (pH 8.5); (d) from about 0.5% to about 2% (w/v) of a suspending agent; (e) up to about 2% (w/v) preservatives; and (f) water q.s. ad 100%. Preferably the aqueous suspension will be made under sterile conditions and no preservatives will be used. Appropriate methods to aseptically prepare paliperidone palmitate are described in WO 2006/114384 which is hereby incorporated by reference herein.

The preferred aqueous dosage form contains inactive ingredients that are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection.

As used herein, a dose or dosing is expressed as milligrams (mg) of paliperidone palmitate. Paliperidone palmitate dosing may also be expressed as mg equivalents (mg eq.) of paliperidone with about 39, 78, 117, 156, and 234 mg of paliperidone palmitate being equivalent to about 25, 50, 75, 100 and 150 mg eq., of paliperidone, respectively. For three month depot dosing it is preferred to dose patients with about 175 mg eq. to about 525 mg eq. paliperidone or about 273 mg to about 819 mg paliperidone palmitate.

The term "antipsychotics" or "antipsychotic drug medication" as used herein means any medication used to decrease or ameliorate the symptoms of psychosis in a person with a psychotic disorder.

The term "psychiatric patient" as used herein, refers to a human, who has been the object of treatment, or experiment for a "mental disorder" and "mental illness" refer to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone esters (e.g. paliperidone palmitate) can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evidenced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform disorders, in DSM-IV-TR such as category 295.xx. Bipolar Disorder refers to a condition characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be associated with psychotic features include, but are not limited to the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress. Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Pre-

JANTZ000000015

PTX-0001\_0015

US 10,143,693 B2

15

dominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusions (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium

16

(292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83). The numbers in parenthesis refer to the DSM-IV-TR categories.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. By way of example, an effective amount of paliperidone for the treatment of mental disorders would be from about 0.01 mg/kg to about 2 mg/kg body weight per day. For monthly depot dosing it is preferred to dose patients with about 25 mg-eq. to about 150 mg eq. paliperidone or about 39 mg to about 234 mg paliperidone palmitate. The amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g. 156 mg corresponds to paliperidone 100 mg). For three month depot dosing it is

JANTZ000000016

PTX-0001\_0016



US 10,143,693 B2

17

preferred to dose patients with about 175 mg eq. to about 525 mg eq. paliperidone or about 273 mg to about 819 mg paliperidone palmitate.

TABLE 3

Conversion between mg PP and mg eq. paliperidone for PP1M and PP3M

PP1M Dose (mg PP)	PP1M Dose (mg eq. Paliperidone)	PP3M Dose (mg PP)	PP3M Dose (mg eq. Paliperidone)
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

PP, paliperidone palmitate;  
PP3M, PP 3-month formulation;  
PP1M, PP 1-month formulation.

The following non-limiting examples are provided to further illustrate the present invention.

## Example 1. Methodology

## Population Pharmacokinetics Models

A comprehensive population pharmacokinetics (PK) model was developed for paliperidone palmitate based on data from previous studies of subjects with schizophrenia. Briefly, a population PK model was developed, using the first-order conditional estimation method (FOCE), to estimate the population PK parameters of paliperidone after single and multiple dose administration of PP3M. The population PK model was constructed using data from a phase-I (NCT01559272) and phase-III study (NCT01529515). The final population PK model was based on 8990 PK samples from 651 patients.

The PP1M and PP3M models were one-compartment models with first-order elimination. In the PP1M absorption sub-model, a fraction of the dose entered the central compartment relatively quickly via a zero-order process. After a certain lag time, the remaining fraction of the dose entered the systemic circulation via a first-order process. The PP3M absorption sub-model consisted of 2 saturable absorption processes.

## Model Based Simulations

The population PK model was used for simulating pre-defined dosing regimen scenarios. Paliperidone plasma concentrations were simulated based on the estimates of the final population PK model using profiles from 5000 patients. The patient population for simulation was built by sampling, with replacement of demographic data from patients in the data set used for the development of PP1M<sup>4</sup> and PP3M models. PK simulations were performed in NONMEM version 7.3.0 and data management/processing of NONMEM output was performed using R 3.0.2 (NONMEM User Guides, Icon Development solutions, Ellicott City, Md.). The population median and 90% prediction interval of the simulated plasma concentration-time profiles were plotted and graphically presented to evaluate the outcome.

## Dosing Windows and Missed Doses

Simulations were performed to assess the dosing window during:

- switching from PP1M (150 or 50 mg eq.) to PP3M (525 or 175 mg eq.) at week 17 and with a  $\pm 1$  week dosing window; and
- maintenance therapy with PP3M (525 or 175 mg eq.) at regular week 12 and with a  $\pm 1$  to 3 week dosing window

18

The paliperidone plasma concentration—time profiles were also simulated for the missed dose scenarios when the third 525 mg eq. PP3M dose was missed and treatment was reinitiated depending on the duration since the last dose.

TABLE 4

Conversion between mg PP and mg eq. paliperidone for PP1M and PP3M

PP1M Dose (mg PP)	PP1M Dose (mg eq. Paliperidone)	PP3M Dose (mg PP)	PP3M Dose (mg eq. Paliperidone)
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

PP, paliperidone palmitate;  
PP3M, PP 3-month formulation;  
PP1M, PP 1-month formulation.

TABLE 5

Dosing reinitiation regimen for the missed dose simulations

Time interval of missed dose	Reinitiation treatment
<4 months	Continue PP3M Q12W
4-9 months	treatment reinitiated with 2 PP1M deltoid injections separated by one week, followed by PP3M dosing Q12W
>9 months	150 mg eq. PP1M deltoid injection on day 1 and 100 mg eq. PP1M deltoid injection on day 8, followed by 3 additional PP1M injections, before continuing PP3M dosing Q12W

Furthermore, paliperidone plasma concentrations versus time after stopping multiple PP3M doses were simulated.

## Assessment of Q12W Vs Q13W

Finally, simulations were also performed to compare Q12W vs Q13W dosing at steady state with PP3M and to demonstrate the impact of actual 3 months dosing (13 weeks) on paliperidone levels.

## Results:

In FIG. 1 the switching from PP1M to PP3M at a default of week 17 $\pm 1$  week resulting in:

TABLE 6

Window	$C_{min}$ (ng/mL)	
+1 week	Reference	11.6
50 mg eq. PP1M Switched to 175 mg eq. PP3M dose	Modified	10.2
-1 week	Reference	58.2
150 mg eq. PP1M Switched to 525 mg eq. PP3M dose	Modified	60.2

As illustrated by FIG. 1 switching from 50 mg eq. PP1M to 175 mg eq. PP3M at Week 18 instead of Week 17 led to a decrease in  $C_{min}$  from 11.6 ng/mL to 10.2 ng/mL, and switching from 150 mg eq. PP1M to 525 mg eq. PP3M at Week 16 instead of Week 17 led to an increase in  $C_{max}$  from 58.2 ng/mL to 60.2 ng/mL. These changes in plasma concentrations are relatively small when a  $\pm 1$  week window is allowed at the time of switching from PP1M to PP3M.

In FIGS. 2A-2B the PP3M with a 12 week dosing week was modeled. In FIG. 2A the -X week simulations were performed with the highest PP3M dose strength of 525 mg eq. to simulate a worst-case scenario (i.e., largest % increase in  $C_{max}$ ).

JANTZ000000017

PTX-0001\_0017

US 10,143,693 B2

19

TABLE 7

525 mg eq. PP3M	$C_{max}$ (ng/mL)
Reference	56.4
Modified (-1 week)	57.1
Modified (-2 week)	58.0
Modified (-3 week)	58.8

In FIG. 2B) the +X week simulations were performed with the lowest PP3M dose strength of 175 mg eq. to simulate a worst-case scenario (i.e., largest % drop in  $C_{min}$ ) since the lowest dose has the shortest apparent  $t_{1/2}$ .

TABLE 8

175 mg eq. PP3M	$C_{min}$ (ng/mL)
Reference	11.0
Modified (+1 week)	10.3
Modified (+2 week)	9.7
Modified (+3 week)	9.0

After stabilization on PP3M, administration of 175 mg eq. PP3M:

- 1 week later than the scheduled:  $C_{min}$  decreased by 0.7 ng/mL.
- 2 weeks later than the scheduled:  $C_{min}$  decreased by 1.3 ng/mL.
- 3 weeks later than the scheduled:  $C_{min}$  decreased by 2.0 ng/mL.

After stabilization on PP3M, administration of 525 mg eq. PP3M,

- 1 week earlier than scheduled:  $C_{max}$  increased by 0.7 ng/mL.
- 2 weeks earlier than scheduled:  $C_{max}$  increased by 1.6 ng/mL.
- 3 weeks earlier than the scheduled:  $C_{max}$  increased by 2.4 ng/mL.

FIG. 2B illustrates the simulations done with 12 weeks with a maximum possible window of +3 weeks. However, 3 months is 13 weeks hence the simulations illustrates 3 months+2 week window. These changes in plasma concentrations are relatively small and justify a  $\pm 3$  week window for Q12W administration of PP3M, which corresponds to a  $\pm 2$  week window for Q13W (i.e. every 3 months) administration.

FIG. 4A-4C illustrate the predicted plasma concentration of PP3M (525 mg. eq.) at various time intervals. Similar paliperidone plasma outcomes were observed for other dosage strengths. Similar paliperidone plasma concentration as before the missed dose was achieved by the following reinitiation treatment:

PP3M missed by <4 months, treatment reinitiated with regular PP3M injections

PP3M missed between 4-9 months, treatment reinitiated with 2 PP1M deltoid injections separated by one week, followed by PP3M dosing Q12W using the regimen described in the table below:

20

TABLE 9

Re-initiation regimen after missing $\geq 4$ months up to 9 months of PP3M				
Last PP3M dose	Administer PP1M, two doses one week apart (into deltoid muscle)		Then administer PP3M (into deltoid <sup>a</sup> or gluteal muscle)	
	Day 1	Day 8	1 month after day 8	
175 mg eq.	50 mg eq.	50 mg eq.	175 mg eq.	
263 mg eq.	75 mg eq.	75 mg eq.	263 mg eq.	
350 mg eq.	100 mg eq.	100 mg eq.	350 mg eq.	
525 mg eq.	100 mg eq.	100 mg eq.	525 mg eq.	

PP3M missed for >9 months, treatment reinitiated with PP1M for 4 months before continuation of PP3M Q12W

Concentration of  $\geq 7.5$  ng/mL was maintained up to 10 to 14 months after the discontinuation of 350 and 525 mg eq. PP3M.

Paliperidone concentration of 7.5 ng/mL is associated with 60%  $D_2$  receptor occupancy, and is thought to be required for antipsychotic efficacy<sup>5</sup>. These simulations therefore support re-initiation with at least 4 months of treatment with PP1M (before transitioning to PP3M) if a maintenance dose of PP3M is missed for more than 9 months.

Additional simulations also showed a similar outcome with other dose strengths (data not shown).

What is claimed is:

1. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with a 3-month injectable paliperidone palmitate depot (PP3M), wherein said patient had been last administered a PP3M injection more than 9 months ago, and the next scheduled maintenance dose of the PP3M should be administered to said patient, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of 150 mg eq. of monthly injectable paliperidone palmitate depot (PP1M);
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of 100 mg eq. of PP1M on about the 4th day to about the 12th day after administering said first reinitiation loading dose;
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a first reinitiation maintenance dose of 50 mg eq. to about 150 mg eq. of PP1M on about the 23th day to about the 37th day after administering said second reinitiation loading dose;
- (4) administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering of the first reinitiation maintenance dose;
- (5) administering intramuscularly in the deltoid or gluteal muscle of said patient a third reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering of the second reinitiation maintenance dose; and
- (6) administering intramuscularly in the deltoid or gluteal muscle of said patient from about 175 mg eq. to about 525 mg eq. of PP3M on about the 23rd day to about the

JANTZ000000018

PTX-0001\_0018

US 10,143,693 B2

21

37th day after administering of the last reinitiation maintenance dose of monthly injectable paliperidone palmitate.

2. The method of claim 1, wherein said patient is in need of treatment for psychosis.

3. The method of claim 1, wherein said patient is in need of treatment for schizophrenia.

4. The method of claim 1, wherein said patient is in need of treatment for bipolar disorder.

5. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of treatment for psychosis, schizophrenia or bipolar disorder that has been treated with PP3M, wherein said patient had been last administered a PP3M injection 4 to 9 months ago and the next scheduled maintenance dose of PP3M should be administered to said patient, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M;
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of PP1M on about the 4th day to about the 12th day after administering of said first reinitiation loading dose; and
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation dose of PP3M on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M wherein said first and second reinitiation loading doses and the reinitiation PP3M dose are selected from the table below based on the amount of the missed dose

Missed Dose of PP3M	Reinitiation Doses of PP1M	Reinitiation Doses of PP3M
175 mg eq.	50 mg eq.	175 mg eq.
263 mg eq.	75 mg eq.	263 mg eq.
350 mg eq.	100 mg eq.	350 mg eq.
525 mg eq.	100 mg eq.	525 mg eq.

6. The method of claim 5, wherein said patient is in need of treatment for psychosis.

7. The method of claim 5, wherein said patient is in need of treatment for schizophrenia.

8. The method of claim 5, wherein said patient is in need of treatment for bipolar disorder.

9. The method of claim 5 wherein the second reinitiation dose of PP1M is administered about 7 days after administering said first reinitiation loading dose of PP1M.

10. The method of claim 9 wherein the second reinitiation dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.

11. The method of claim 5 wherein the reinitiation dose of PP3M is administered about 30 days after administering said second reinitiation loading dose of PP1M.

12. The method of claim 11 wherein the reinitiation dose of PP3M is administered 30 days after administering said second reinitiation loading dose of PP1M.

13. The method of claim 5 wherein the reinitiation dose of PP3M is administered about a month after administering said second reinitiation loading dose of PP1M.

22

14. The method of claim 11 wherein the reinitiation dose of PP3M is administered a month after administering said second reinitiation loading dose of PP1M.

15. The method of claim 1 wherein the second reinitiation loading dose of PP1M is administered about 7 days after administering said first reinitiation loading dose of PP1M.

16. The method of claim 15 wherein the second reinitiation loading dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.

17. The method of claim 1 wherein the first reinitiation maintenance dose of PP1M is administered about 30 days after administering said second reinitiation loading dose of PP1M.

18. The method of claim 1 wherein the first reinitiation maintenance dose of PP1M is administered 30 days after administering said second reinitiation loading dose of PP1M.

19. The method of claim 1 wherein the second reinitiation maintenance of PP1M is administered about 30 days after administering said first reinitiation maintenance dose of PP1M.

20. The method of claim 1 wherein the second reinitiation maintenance of PP1M is administered 30 days after administering said first reinitiation maintenance dose of PP1M.

21. The method of claim 1 wherein the third reinitiation maintenance of PP1M is administered about 30 days after administering said second reinitiation maintenance dose of PP1M.

22. The method of claim 1 wherein the third reinitiation maintenance of PP1M is administered 30 days after administering said second reinitiation maintenance dose of PP1M.

23. The method of claim 1 wherein PP3M is administered about 30 days after administering said last reinitiation maintenance of PP1M.

24. The method of claim 1 wherein PP3M is administered 30 days after administering said last reinitiation maintenance of PP1M.

25. The method of claim 1 wherein PP3M is administered about a month after administering said last reinitiation maintenance of PP1M.

26. The method of claim 1 wherein PP3M is administered a month after administering said last reinitiation maintenance of PP1M.

27. The method of claim 1 further comprising administering intramuscularly in the deltoid or gluteal muscle of said patient a fourth reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering the third reinitiation maintenance dose.

28. The method of claim 27 wherein said fourth reinitiation maintenance of PP1M is administered about 30 days after administering said third reinitiation maintenance dose of PP1M.

29. The method of claim 28 wherein said fourth reinitiation maintenance of PP1M is administered 30 days after administering said third reinitiation maintenance dose of PP1M.

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PTX-0001\_0019

PTX-0043

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use INVEGA TRINZA™ safely and effectively. See full prescribing information for INVEGA TRINZA™.

INVEGA TRINZA™ (paliperidone palmitate) extended-release injectable suspension, for intramuscular use  
Initial U.S. Approval: 2006

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. (5.1)
- INVEGA TRINZA™ is not approved for use in patients with dementia-related psychosis. (5.1)

**INDICATIONS AND USAGE**

INVEGA TRINZA™, a 3-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in patients after they have been adequately treated with INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension) for at least four months. (1)

**DOSAGE AND ADMINISTRATION**

- Use INVEGA TRINZA™ only after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least four months. (2.2)
- INVEGA TRINZA™ should be administered once every 3 months. (2.1)
- For intramuscular injection only. (2.1)
- Each injection must be administered only by a health care professional. (2.1)
- For deltoid injection: For patients weighing less than 90 kg, use the 1-inch 22 gauge thin wall needle. For patients weighing 90 kg or more, use the 1½-inch 22 gauge thin wall needle.
- For gluteal injection: Regardless of patient weight, use the 1½-inch 22 gauge thin wall needle.
- Prior to administration, shake the prefilled syringe vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension. (2.1)
- Initiate INVEGA TRINZA™ when the next 1-month paliperidone palmitate dose is scheduled with an INVEGA TRINZA™ dose based on the previous 1-month injection dose as shown below. (2.2)

**INVEGA TRINZA™ Doses for Adult Patients Adequately Treated with INVEGA SUSTENNA®**

If the Last Dose of INVEGA SUSTENNA® is:	Initiate INVEGA TRINZA™ at the Following Dose:
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the INVEGA SUSTENNA® 39 mg dose was not studied.

- Missed Doses: Missing doses of INVEGA TRINZA™ should be avoided. To manage missed doses on exceptional occasions, refer to the Full Prescribing Information. (2.3)
- Moderate to severe renal impairment (creatinine clearance < 50 mL/min): INVEGA TRINZA™ is not recommended. (2.5)
- Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Adjust dosage and stabilize the patient using INVEGA SUSTENNA®, then transition to INVEGA TRINZA™. See above table. (2.5)

**DOSAGE FORMS AND STRENGTHS**

Extended-release injectable suspension: 273 mg, 410 mg, 546 mg, or 819 mg (3)

**CONTRAINDICATIONS**

Known hypersensitivity to paliperidone, risperidone, or to any excipients in the formulation (4)

**WARNINGS AND PRECAUTIONS**

- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:** Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). INVEGA TRINZA™ is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation of drug and close monitoring (5.3)
- QT Prolongation:** Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)
- Tardive Dyskinesia:** Discontinue drug if clinically appropriate (5.5)
- Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
  - Hyperglycemia and Diabetes Mellitus:** Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
  - Dyslipidemia:** Undesirable alterations have been observed. (5.6)
  - Weight Gain:** Significant weight gain has been reported. Monitor weight gain. (5.6)
- Orthostatic Hypotension and Syncope:** Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis:** Monitor complete blood count in patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.8)
- Hyperprolactinemia:** Prolactin elevations occur and persist during chronic administration (5.9)
- Potential for Cognitive and Motor Impairment:** Use caution when operating machinery (5.10)
- Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.11)

**ADVERSE REACTIONS**

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

**DRUG INTERACTIONS**

**Strong CYP3A4/P-glycoprotein (P-gp) inducers:** Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during a dosing interval for INVEGA TRINZA™. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets. (7.2, 12.3)

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2015



**FULL PRESCRIBING INFORMATION****WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS  
WITH DEMENTIA-RELATED PSYCHOSIS**

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death *[see Warnings and Precautions (5.1)]*.
- INVEGA TRINZA™ is not approved for use in patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

**1 INDICATIONS AND USAGE**

INVEGA TRINZA™ (paliperidone palmitate), a 3-month injection, is indicated for the treatment of schizophrenia in patients after they have been adequately treated with INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension) for at least four months *[see Dosage and Administration (2.2) and Clinical Studies (14)]*.

**2 DOSAGE AND ADMINISTRATION****2.1 Administration Instructions**

INVEGA TRINZA™ should be administered once every 3 months.

Each injection must be administered only by a health care professional.

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration. **It is important to shake the syringe vigorously for at least 15 seconds to ensure a homogeneous suspension. Inject INVEGA TRINZA™ within 5 minutes of shaking vigorously** *[see Dosage and Administration (2.8)]*.

INVEGA TRINZA™ is intended for intramuscular use only. Do not administer by any other route. Avoid inadvertent injection into a blood vessel. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the deltoid or gluteal muscle.

INVEGA TRINZA™ must be administered using only the thin wall needles that are provided in the INVEGA TRINZA™ pack. Do not use needles from the 1-month paliperidone palmitate extended-release injectable suspension pack or other commercially-available needles to reduce the risk of blockage.

**Deltoid Injection**

The recommended needle size for administration of INVEGA TRINZA™ into the deltoid muscle is determined by the patient's weight:

- For patients weighing less than 90 kg, the 1-inch, 22 gauge thin wall needle is recommended.



- For patients weighing 90 kg or more, the 1½-inch, 22 gauge thin wall needle is recommended.

Administer into the center of the deltoid muscle. Deltoid injections should be alternated between the two deltoid muscles.

#### Gluteal Injection

Regardless of patient weight, the recommended needle size for administration of INVEGA TRINZA™ into the gluteal muscle is the 1½-inch, 22 gauge thin wall needle. Administer into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be alternated between the two gluteal muscles.

#### Incomplete Administration

To avoid an incomplete administration of INVEGA TRINZA™, ensure that the prefilled syringe is **shaken vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension and ensure the needle does not get clogged during injection** [see *Dosage and Administration* (2.8)].

However, in the event of an incompletely administered dose, do **not** re-inject the dose remaining in the syringe and do **not** administer another dose of INVEGA TRINZA™. Closely monitor and treat the patient with oral supplementation as clinically appropriate until the next scheduled 3-month injection of INVEGA TRINZA™.

## 2.2 Schizophrenia

### Adults

INVEGA TRINZA™ is to be used only after INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension) has been established as adequate treatment for at least four months. In order to establish a consistent maintenance dose, it is recommended that the last two doses of INVEGA SUSTENNA® be the same dosage strength before starting INVEGA TRINZA™.

Initiate INVEGA TRINZA™ when the next 1-month paliperidone palmitate dose is scheduled with an INVEGA TRINZA™ dose based on the previous 1-month injection dose, using the equivalent 3.5-fold higher dose as shown in Table 1. INVEGA TRINZA™ may be administered up to 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.

**Table 1. INVEGA TRINZA™ Doses for Adult Patients Adequately Treated with INVEGA SUSTENNA®**

<b>If the Last Dose of INVEGA SUSTENNA® is:</b>	<b>Initiate INVEGA TRINZA™ at the Following Dose:</b>
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the INVEGA SUSTENNA® 39 mg dose was not studied.

Following the initial INVEGA TRINZA™ dose, INVEGA TRINZA™ should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 273 mg to 819 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of INVEGA TRINZA™, the patient's response to an adjusted dose may not be apparent for several months [*see Clinical Pharmacology (12.3)*].

### **2.3 Missed Doses**

#### **Dosing Window**

Missing doses of INVEGA TRINZA™ should be avoided. If necessary, patients may be given the injection up to 2 weeks before or after the 3-month time point.

#### **Missed Dose 3½ Months to 4 Months Since Last Injection**

If more than 3½ months (up to but less than 4 months) have elapsed since the last injection of INVEGA TRINZA™, the previously administered INVEGA TRINZA™ dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

#### **Missed Dose 4 Months to 9 Months Since Last Injection**

If 4 months up to and including 9 months have elapsed since the last injection of INVEGA TRINZA™, do NOT administer the next dose of INVEGA TRINZA™. Instead, use the re-initiation regimen shown in Table 2.

**Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of INVEGA TRINZA™**

If the Last Dose of INVEGA TRINZA™ was:	Administer INVEGA SUSTENNA®, two doses one week apart (into deltoid muscle)		Then administer INVEGA TRINZA™ (into deltoid <sup>a</sup> or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

<sup>a</sup> See Instructions for Use for deltoid injection needle selection based on body weight.

### Missed Dose Longer than 9 Months Since Last Injection

If more than 9 months have elapsed since the last injection of INVEGA TRINZA™, re-initiate treatment with the 1-month paliperidone palmitate extended-release injectable suspension as described in the prescribing information for that product. INVEGA TRINZA™ can then be resumed after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least 4 months.

### 2.4 Use with Risperidone or with Oral Paliperidone

Since paliperidone is the major active metabolite of risperidone, caution should be exercised when INVEGA TRINZA™ is coadministered with risperidone or oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA TRINZA™ with other antipsychotics is limited.

### 2.5 Dosage Adjustment in Renal Impairment

INVEGA TRINZA™ has not been systematically studied in patients with renal impairment [*see Clinical Pharmacology (12.3)*]. For patients with mild renal impairment (creatinine clearance  $\geq 50$  mL/min to  $< 80$  mL/min [Cockcroft-Gault Formula], adjust dosage and stabilize the patient using the 1-month paliperidone palmitate extended-release injectable suspension, then transition to INVEGA TRINZA™ [*see Table 1, Dosage and Administration (2.2)*]. [*See also Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]

INVEGA TRINZA™ is not recommended in patients with moderate or severe renal impairment (creatinine clearance  $< 50$  mL/min) [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

## 2.6 Switching from INVEGA TRINZA™ to the 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension

For switching from INVEGA TRINZA™ to INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension), the 1-month paliperidone palmitate extended-release injectable suspension should be started 3 months after the last INVEGA TRINZA™ dose, using the equivalent 3.5-fold lower dose as shown in Table 3. The 1-month paliperidone palmitate extended-release injectable suspension should then continue, dosed at monthly intervals.

**Table 3. Conversion From INVEGA TRINZA™ to INVEGA SUSTENNA®**

<b>If the Last Dose of INVEGA TRINZA™ is:</b>	<b>Initiate<sup>a</sup> INVEGA SUSTENNA® 3 Months Later at the Following Dose:</b>
273 mg	78 mg
410 mg	117 mg
546 mg	156 mg
819 mg	234 mg

<sup>a</sup> The initiation dosing as described in the prescribing information for INVEGA SUSTENNA® is not required.

## 2.7 Switching from INVEGA TRINZA™ to Oral Paliperidone Extended-Release Tablets

For switching from INVEGA TRINZA™ to oral paliperidone extended-release tablets, the daily dosing of the paliperidone extended-release tablets should be started 3 months after the last INVEGA TRINZA™ dose and transitioned over the next several months following the last INVEGA TRINZA™ dose as described in Table 4. Table 4 provides dose conversion regimens to allow patients previously stabilized on different doses of INVEGA TRINZA™ to attain similar paliperidone exposure with once daily paliperidone extended-release tablets.

**Table 4. INVEGA TRINZA™ Doses and Once-Daily Paliperidone Extended-Release Conversion Regimens Needed to Attain Similar Paliperidone Exposures**

	<b>Weeks Since Last INVEGA TRINZA™ Dose</b>		
	<b>3 months to 18 weeks</b>	<b>Longer than 18 weeks to 24 weeks</b>	<b>Longer than 24 weeks</b>
<b>Last INVEGA TRINZA™ Dose</b>	<b>Doses of oral paliperidone extended-release tablets</b>		
273 mg	3 mg	3 mg	3 mg
410 mg	3 mg	3 mg	6 mg
546 mg	3 mg	6 mg	9 mg
819 mg	6 mg	9 mg	12 mg

**Dispose properly**

Dispose of the syringe and unused needle in an approved sharps container.



Thin wall safety needles are designed specifically for use with INVEGA TRINZA™. Unused needle should be discarded and not saved for future use.

**3 DOSAGE FORMS AND STRENGTHS**

INVEGA TRINZA™ is available as a white to off-white aqueous extended-release injectable suspension for intramuscular injection in dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate.

**4 CONTRAINDICATIONS**

INVEGA TRINZA™ is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA TRINZA™ formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. Paliperidone palmitate is converted to paliperidone, which is a metabolite of risperidone.

**Table 6. Change in Fasting Lipids from the Long-Term Maintenance Trial with INVEGA TRINZA™ in Subjects with Schizophrenia**

	Open-Label Phase (relative to open-label baseline)	Double-Blind Phase (relative to double-blind baseline)	
	Paliperidone Palmitate <sup>a</sup>	Placebo	INVEGA TRINZA™
	Mean change from baseline (mg/dL)		
<b>Cholesterol</b>	<b>n=400</b>	<b>n=120</b>	<b>n=138</b>
Change from baseline	0.5	-0.4	0.9
<b>LDL</b>	<b>n=396</b>	<b>n=119</b>	<b>n=138</b>
Change from baseline	1.1	-0.4	1.1
<b>HDL</b>	<b>n=397</b>	<b>n=119</b>	<b>n=138</b>
Change from baseline	-0.2	-0.5	-1.3
<b>Triglycerides</b>	<b>n=400</b>	<b>n=120</b>	<b>n=138</b>
Change from baseline	0.1	-2.0	5.1
	Proportion of Patients with Shifts		
<b>Cholesterol Normal to High</b> ( $<200$ mg/dL to $\geq 240$ mg/dL)	2.0% (8/400)	3.9% (5/128)	1.4% (2/148)
<b>LDL Normal to High</b> ( $<100$ mg/dL to $\geq 160$ mg/dL)	0.3% (1/396)	0.8% (1/127)	0% (0/148)
<b>HDL Normal to Low</b> ( $\geq 40$ mg/dL to $<40$ mg/dL)	8.6% (34/397)	9.4% (12/127)	13.5% (20/148)
<b>Triglycerides Normal to High</b> ( $<150$ mg/dL to $\geq 200$ mg/dL)	4.5% (18/400)	1.6% (2/128)	8.1% (12/148)

<sup>a</sup> During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate extended-release injectable suspension followed by a single dose of INVEGA TRINZA™ [see Clinical Studies (14)].

### Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Data on mean changes in body weight and the proportion of subjects meeting a weight gain criterion of  $\geq 7\%$  of body weight from the long-term maintenance trial with INVEGA TRINZA™ in subjects with schizophrenia are presented in Table 7.



**Table 7. Change in Body Weight (kg) and the Proportion of Subjects with  $\geq 7\%$  Gain in Body Weight from the Long-Term Maintenance Trial with INVEGA TRINZA™ in Subjects with Schizophrenia**

	Open-Label Phase (relative to open-label baseline)	Double-Blind Phase (relative to double-blind baseline)	
	Paliperidone Palmitate <sup>a</sup>	Placebo	INVEGA TRINZA™
	n=466	n=142	n=157
Weight (kg) Change from baseline	1.42	-1.28	0.94
Weight Gain $\geq 7\%$ increase from baseline	15.2%	0.7%	9.6%

<sup>a</sup> During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate extended-release injectable suspension followed by a single dose of INVEGA TRINZA™ [see *Clinical Studies (14)*].

### 5.7 Orthostatic Hypotension and Syncope

Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-adrenergic blocking activity. In the long-term maintenance trial, syncope was reported in  $< 1\%$  (1/506) of subjects treated with the 1-month paliperidone palmitate extended-release injectable suspension during the open-label phase; there were no cases reported during the double-blind phase in either treatment group. In the long-term maintenance trial, orthostatic hypotension was reported as an adverse event by  $< 1\%$  (1/506) of subjects treated with the 1-month paliperidone palmitate extended-release injectable suspension and  $< 1\%$  (1/379) of subjects after receiving a single-dose of INVEGA TRINZA™ during the open-label phase; there were no cases reported during the double-blind phase in either treatment group.

INVEGA TRINZA™ should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

### 5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including INVEGA TRINZA™. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or a drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few

Paliperidone palmitate showed no genotoxicity in the *in vitro* Ames bacterial reverse mutation test and mouse lymphoma assay. Paliperidone was not genotoxic in the *in vitro* Ames bacterial reverse mutation test, mouse lymphoma assay and the *in vivo* rat bone marrow micronucleus test.

#### Impairment of Fertility

No fertility studies were conducted with the 3-month paliperidone palmitate extended-release injectable suspension.

In a rat fertility study orally administered paliperidone increased pre- and post-implantation losses and slightly decreased the number of live embryos at doses up to 2.5 mg/kg/day, a dose which is 2 times the MRHD of 12 mg on mg/m<sup>2</sup> basis. This dose also caused slight maternal toxicity but there was no effect on the percentage of treated female rats that became pregnant. Pre- and post- implantation losses, the number of live embryos and maternal toxicity were not affected at 0.63 mg/kg/day, a dose, which is half of the MRHD of 12 mg/day of orally administered paliperidone on mg/m<sup>2</sup> basis. The fertility of male rats was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day, which are up to 2 times the MRHD of 12 mg on mg/m<sup>2</sup> basis, although sperm count and sperm viability studies were not conducted with paliperidone.

In a sub-chronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested 0.31 to 5.0 mg/kg/day, which are 0.6 to 10 times the MRHD of 16 mg on mg/m<sup>2</sup> basis, resulted in decreases in serum testosterone and decreases in sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased at the last observation two months after treatment was discontinued.

### 13.2 Animal Toxicology and/or Pharmacology

Injection site toxicity was assessed in minipigs injected intramuscularly with the 3-month paliperidone palmitate extended-release injectable suspension at doses up to 819 mg, which is equal to the MRHD. Injection site inflammatory reactions were greater and more advanced than reactions to the 1-month paliperidone palmitate extended-release injectable suspension. Reversibility of these findings was not examined.

## 14 CLINICAL STUDIES

The efficacy of INVEGA TRINZA™ for the treatment of schizophrenia in patients who have been adequately treated for at least 4 months with INVEGA SUSTENNA® (1-month paliperidone palmitate extended-release injectable suspension) was evaluated in a long-term double-blind, placebo-controlled randomized-withdrawal trial designed to evaluate time to relapse involving adult subjects who met DSM-IV-TR criteria for schizophrenia.



Patients could enter the study with acute symptoms (if previously treated with oral antipsychotics) or be clinically stable (if treated with long-acting injectable antipsychotics [LAI]). All patients who previously received oral antipsychotics received the paliperidone palmitate 1-month initiation regimen (deltoid injections of 234 mg and 156 mg one week apart), while those patients switching from LAI medication were treated with the 1-month paliperidone palmitate extended-release injectable suspension in place of the next scheduled injection. Specifically:

- For patients entering the study who were already being treated with the 1-month paliperidone palmitate extended-release injectable suspension, their dosing remained unchanged. Patients who were currently receiving the 39 mg dose of 1-month paliperidone palmitate were not eligible to enroll in the study.
- Patients entering the study who were being treated with 25 mg, 37.5 mg, or 50 mg of RISPERDAL CONSTA<sup>®</sup> (risperidone long-acting injection) were switched to 78 mg, 117 mg, or 156 mg, respectively, of the 1-month paliperidone palmitate administered in the deltoid muscle.
- Patients entering the study who were being treated with any other LAI product were switched to 234 mg of the 1-month paliperidone palmitate administered in the deltoid muscle.

This study consisted of the following three treatment periods:

- A 17-week flexible-dose open-label period with the 1-month paliperidone palmitate (first part of a 29-week open-label stabilization phase). A total of 506 patients entered this phase of the study. Dosing of the 1-month paliperidone palmitate was individualized based on symptom response, tolerability, and previous medication history. Specifically, the dose could be adjusted at the week 5 and 9 injections and the injection site could be deltoid or gluteal. The week 13 dose had to be the same as the week 9 dose. Patients had to be clinically stable at the end of this period before receiving INVEGA TRINZA<sup>™</sup> at the week 17 visit. Clinical stability was defined as achieving a PANSS total score <70 at week 17. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210.
- A 12-week open-label treatment period with INVEGA TRINZA<sup>™</sup> (second part of a 29-week open-label stabilization phase). A total of 379 patients received a single-dose of INVEGA TRINZA<sup>™</sup> which was a 3.5 multiple of the last dose of the 1-month paliperidone palmitate. Patients had to remain clinically stable before entry into the next period (double-blind).

Clinical stability was defined as achieving a PANSS total score  $<70$  and scores of  $\leq 4$  for seven specific PANSS items.

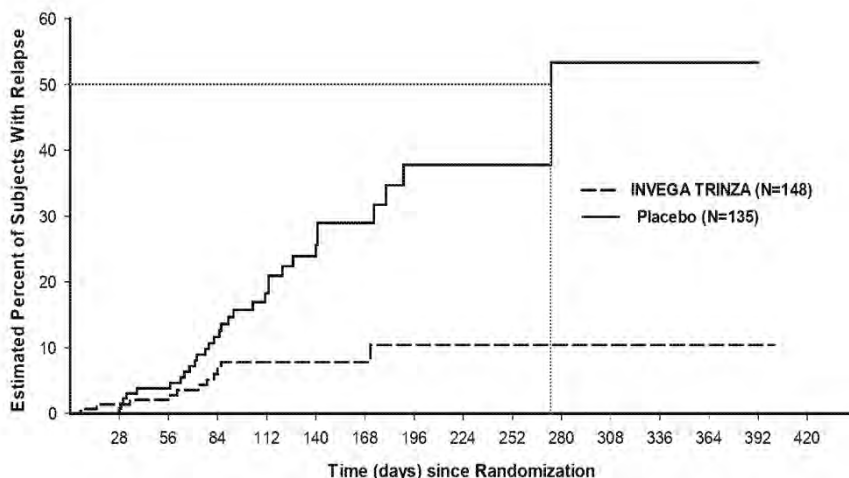
- A variable length double-blind treatment period. In this period, 305 stabilized patients were randomized 1:1 to continue treatment with INVEGA TRINZA™ or placebo until relapse, early withdrawal, or the end of study. Patients were randomized to the same dose of INVEGA TRINZA™ they received during the open-label phase (i.e., 273 mg, 410 mg, 546 mg, or 819 mg) or to placebo administered every 12 weeks. The numbers (%) of patients entering double-blind on each of the dose levels were 6 (4%) for 273 mg, 15 (9%) for 410 mg, 78 (49%) for 546 mg, and 61 (38%) for 819 mg.

The primary efficacy variable was time to first relapse. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization,  $\geq 25\%$  increase (if the baseline score was  $> 40$ ) or a 10-point increase (if the baseline score was  $\leq 40$ ) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of  $\geq 5$  (if the maximum baseline score was  $\leq 3$ ) or  $\geq 6$  (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items.

A pre-planned interim analysis showed a statistically significantly longer time to relapse in patients treated with INVEGA TRINZA™ compared to placebo, and the study was stopped early because efficacy was demonstrated. The most common reason for relapse observed across both treatment groups was increase in the PANSS total score value, followed by psychiatric hospitalization.

Twenty-three percent (23%) of patients in the placebo group and 7.4% of patients in the INVEGA TRINZA™ group experienced a relapse event. The time to relapse was statistically significantly longer in patients randomized to the INVEGA TRINZA™ group than compared to placebo-treated patients. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 4.

An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

**Figure 4:** Kaplan-Meier Plot of Cumulative Proportion of Patients with Relapse<sup>a</sup> Over Time – Interim Analysis.

<sup>a</sup> The median time to relapse in the placebo group was 274 days. The median time to relapse in the INVEGA TRINZA™ group could not be estimated due to low percentage (7.4%) of subjects with relapse.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

INVEGA TRINZA™ is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate. The kit contains a prefilled syringe and 2 safety needles (a thin walled 22G, 1-inch safety needle and a thin walled 22G, 1½-inch safety needle).

273 mg paliperidone palmitate kit (NDC 50458-606-01)

410 mg paliperidone palmitate kit (NDC 50458-607-01)

546 mg paliperidone palmitate kit (NDC 50458-608-01)

819 mg paliperidone palmitate kit (NDC 50458-609-01)

### Storage and Handling

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F and 86°F) are permitted.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

### Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal side effect referred to as Neuroleptic Malignant Syndrome (NMS) that has been reported in association with administration of antipsychotic

PTX-0089C

HIGHLY CONFIDENTIAL

## EXHIBIT 3

## SUMMARY OF THE PATENT-IN-SUIT AND OTHER PATENTS RELATED TO INVEGA TRINZA OR PALIPERIDONE PALMITATE

Patent-in-Suit							Issuance by FDA Orange Book for Invega Trinza						
Patent Number	Title	Filing Date	Issue Date	Expiration Date	Related U.S. Applications	Abstract	2015	2016	2017	2018	2019	2020	2021
[1] U.S. 10,143,693	Dosing Regimen for Missed Doses for Long-Acting Injectable Paliperidone Esters	Apr. 5, 2016	Dec. 4, 2018	Apr. 5, 2036	Prior Publication: US 2017/0281629 A1 filed Oct. 5, 2017. Related provisional applications: No. 62/162,596 and No. 62/144,054, filed on May 15, 2015 and Apr. 7, 2015, respectively.	The present application provides a method for treating patients in need of psychiatric treatment, wherein said patient is being treated with the 3-month formulation of paliperidone palmitate and fails to take the next scheduled dose of the 3-month formulation of paliperidone palmitate.					X	X	X
Other Patents Related to Invega Trinza Or Paliperidone Palmitate							Issuance by FDA Orange Book for Invega Trinza						
Patent Number	Title	Filing Date	Issue Date	Expiration Date	Related U.S. Applications	Abstract	2015	2016	2017	2018	2019	2020	2021
[2] U.S. 5,254,556	3-Piperidinyl-1,2-Benzisoxazoles	Aug. 19, 1992	Oct. 19, 1993	Oct. 27, 2012 Apr. 27, 2013 (*PED)	Division of Ser. No. 422,847, Oct. 17, 1989, Pat. No. 5,158,952, which is a continuation-in-part of Ser. No. 267,857, Nov. 7, 1988, abandoned.	The invention relates to [certain] alkanolic acid esters [], pharmaceutically acceptable acid addition salts thereof, and enantiomeric forms thereof, which are useful in the treatment of warm-blooded animals suffering from psychotic diseases.							
[3] U.S. 6,077,843	Aqueous Suspensions of 9-Hydroxyrisperidone Fatty Acid Esters	May 12, 1997	Jun. 20, 2000	May 12, 2017 Nov. 12, 2017 (*PED)		The present invention is concerned with a pharmaceutical composition suitable as a depot formulation for administration via intramuscular or subcutaneous injection, comprising: (1) as an active ingredient a therapeutically effective amount of a 9-hydroxyrisperidone fatty acid ester or a salt, or a stereoisomer or a stereoisomeric mixture thereof and (2) a pharmaceutically acceptable carrier; wherein the pharmaceutically acceptable carrier is water and the active ingredient is suspended therein; and with a process of preparing such a composition. The invention further concerns such a pharmaceutical composition for use as a medicament in the treatment of schizophrenia, non-schizophrenic psychoses, behavioral disturbances associated with neurodegenerative disorders, e.g. in dementia, behavioral disturbances in mental retardation and autism, bipolar mania, depression, anxiety.		X	X	X			

Notes & Sources:

- \* PED refers to pediatric exclusivity expiration date. See <https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity> (viewed 4/20/2022).
- Orange Book Issuances from FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 35th Edition, 2015, at ADA 164-165; FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 36th Edition, 2016, at ADA 165; FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 37th Edition, 2017, at ADA 176-177; FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 38th Edition, 2018, at ADA 197; FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 39th Edition, 2019, at ADA 198-199; FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 40th Edition, 2020, at ADA 211-212; FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 41st Edition, 2021, at ADA 227; FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 42nd Edition, 2022, at ADA 226.
- U.S. Patent No. 5,254,556 covers the paliperidone compound but was not listed in the Orange Book for Invega Trinza as it expired prior to Invega Trinza's launch.
- [1] From U.S. Patent No. 10,143,693; <https://patents.google.com/patent/US10143693B2/en?q=10%2c143%2c693> (viewed 4/12/2022); FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 42nd Edition, 2022, at ADA 226.
- [2] From U.S. Patent No. 5,254,556; <https://patents.google.com/patent/US5254556A/en> (viewed 4/25/2022); FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 32nd Edition, 2012, at ADA 148-149.
- [3] From U.S. Patent No. 6,077,843; <https://patents.google.com/patent/US6077843A/en> (viewed 4/14/2022); FDA, "Approved Drug Products with Therapeutic Equivalence Evaluations," 36th Edition, 2016, at ADA 165.

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HIGHLY CONFIDENTIAL

**EXHIBIT 10****FDA-APPROVED ANTIPSYCHOTIC MEDICATIONS**

Brand Name	Molecule	Date of First Approval	Available as Generic	Indications			Route of Administration		
				Schizophrenia	Schizoaffective Disorder	Other	Oral	Injection	Other
[A]	[B]	[C]	[D]	[E]	[F]	[G]	[H]	[I]	[J]
<b>Long-Acting</b>									
<b>Typical</b>									
[48]	Prolixin Decanoate	Fluphenazine Decanoate	6/20/1972	X	X			X	
[49]	Haldol Decanoate	Haloperidol Decanoate	1/14/1986	X	X			X	
<b>Atypical</b>									
[50]	Risperdal Consta	Risperidone	10/29/2003	X		X		X	
[51]	Invega Sustenna	Paliperidone Palmitate	7/31/2009	X	X			X	
[52]	Zyprexa Relprevv	Olanzapine Pamoate	12/11/2009	X				X	
[53]	Abilify Maintena	Aripiprazole	2/28/2013	X		X		X	
[54]	Invega Trinza	Paliperidone Palmitate	5/18/2015	X				X	
[55]	Aristada	Aripiprazole Lauroxil	10/5/2015	X				X	
[56]	Aristada Initio	Aripiprazole Lauroxil	6/29/2018	X				X	
[57]	Perseris	Risperidone	7/27/2018	X				X	
[58]	Invega Hafyera	Paliperidone Palmitate	8/30/2021	X				X	

Notes & Sources:

[C] All approval dates come from the "Drugs@FDA: FDA Approved Drug Products" database, available at <https://www.accessdata.fda.gov/scripts/cder/daf/>.

For molecules with different forms, which have different approval dates, the earliest approval date is used.

[E]-[G] Includes only indications specifically referenced in the "Indications and Usage" section of the FDA labels.

[D][44] Generic oral Aripiprazole is available (*see* [30]), but there is no generic version containing the sensor technology present Abilify Mycite.

[J][1] Rectal Suppository.

[J][4] Rectal Suppository.

[J][5] Rectal Suppository.

[J][21] Rectal Suppository.

[J][45] Transdermal System.

[1] From <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=010571> (viewed 7/11/2019);  
<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=040101> (viewed 8/8/2019);  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2005/010571s096lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/010571s096lbl.pdf) (viewed 6/27/2019).

[2] From <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=010775> (viewed 6/21/2019);  
<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=011213> (viewed 6/21/2019);  
<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=040226> (viewed 6/24/2019);  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2002/10775s311213s24lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/10775s311213s24lbl.pdf) (viewed 4/22/2021).



PTX-0092

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use **PALIPERIDONE PALMITATE EXTENDED-RELEASE INJECTABLE SUSPENSION** safely and effectively. See full prescribing information for **PALIPERIDONE PALMITATE EXTENDED-RELEASE INJECTABLE SUSPENSION**.

**PALIPERIDONE PALMITATE extended-release injectable suspension, for intramuscular use**  
Initial U.S. Approval: 2006

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

*See full prescribing information for complete boxed warning.*

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. **Paliperidone palmitate is not approved for use in patients with dementia-related psychosis. (5.1)**

**RECENT MAJOR CHANGES**

Warnings and Precautions (5.3, 5.5) 2/2021

**INDICATIONS AND USAGE**

Paliperidone palmitate extended-release injectable suspension, a 3-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in patients after they have been adequately treated with 1-month paliperidone palmitate extended-release injectable suspension for at least four months. (1)

**DOSAGE AND ADMINISTRATION**

- Use 3-month paliperidone palmitate extended-release injectable suspension only after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least four months. (2.2)
- Paliperidone palmitate extended-release injectable suspension should be administered once every 3 months. (2.1)
- For intramuscular injection only. (2.1)
- Each injection must be administered only by a healthcare professional. (2.1)
- For deltoid injection: For patients weighing less than 90 kg, use the 1-inch 22 gauge thin wall needle. For patients weighing 90 kg or more, use the 1½-inch 22 gauge thin wall needle.
- For gluteal injection: Regardless of patient weight, use the 1½-inch 22 gauge thin wall needle.
- Prior to administration, shake the prefilled syringe vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension. (2.1)
- Initiate 3-month paliperidone palmitate when the next 1-month paliperidone palmitate dose is scheduled with a 3-month paliperidone palmitate dose based on the previous 1-month injection dose as shown below. (2.2)

**3-Month Paliperidone Palmitate Extended-Release Injectable Suspension Doses for Adult Patients Adequately Treated with 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension**

If the Last Dose of 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension is:	Initiate 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension at the Following Dose:
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the paliperidone palmitate extended-release injectable suspension 39 mg dose was not studied.

- Missed Doses: Missing doses of paliperidone palmitate extended-release injectable suspension should be avoided. To manage missed doses on exceptional occasions, refer to the Full Prescribing Information. (2.3)
- Moderate to severe renal impairment (creatinine clearance < 50 mL/min): Paliperidone palmitate extended-release injectable suspension is not recommended. (2.5)

- Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Adjust dosage and stabilize the patient using 1-month paliperidone palmitate extended-release injectable suspension, then transition to 3-month paliperidone palmitate extended-release injectable suspension. See above table. (2.5)

**DOSAGE FORMS AND STRENGTHS**

Extended-release injectable suspension: 273 mg, or 410 mg (3)

**CONTRAINDICATIONS**

Known hypersensitivity to paliperidone, risperidone, or to any excipients in paliperidone palmitate extended-release injectable suspension. (4)

**WARNINGS AND PRECAUTIONS**

- **Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:** Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). Paliperidone palmitate extended-release injectable suspension is not approved for use in patients with dementia-related psychosis (5.2)
- **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation of drug and close monitoring (5.3)
- **QT Prolongation:** Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)
- **Tardive Dyskinesia:** Discontinue drug if clinically appropriate (5.5)
- **Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
  - **Hyperglycemia and Diabetes Mellitus:** Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
  - **Dyslipidemia:** Undesirable alterations have been observed. (5.6)
  - **Weight Gain:** Significant weight gain has been reported. Monitor weight gain. (5.6)
- **Orthostatic Hypotension and Syncope:** Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.7)
- **Leukopenia, Neutropenia, and Agranulocytosis:** Monitor complete blood count in patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.9)
- **Hyperprolactinemia:** Prolactin elevations occur and persist during chronic administration (5.10)
- **Potential for Cognitive and Motor Impairment:** Use caution when operating machinery (5.11)
- **Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.12)

**ADVERSE REACTIONS**

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

**Strong CYP3A4/P-glycoprotein (P-gp) inducers:** Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during a dosing interval for paliperidone palmitate extended-release injectable suspension. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets. (7.2, 12.3)

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

## FULL PRESCRIBING INFORMATION

### **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Paliperidone palmitate is not approved for use in patients with dementia-related psychosis. [see Warnings and Precautions (5.1)].**

## **1 INDICATIONS AND USAGE**

Paliperidone palmitate extended-release injectable suspension, a 3-month injection, is indicated for the treatment of schizophrenia in patients after they have been adequately treated with 1-month paliperidone palmitate extended-release injectable suspension for at least four months [see Dosage and Administration (2.2) and Clinical Studies (14)].

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Administration Instructions**

Paliperidone palmitate extended-release injectable suspension should be administered once every 3 months.

Each injection must be administered only by a healthcare professional.

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration. **It is important to shake the syringe vigorously for at least 15 seconds to ensure a homogeneous suspension. Inject paliperidone palmitate extended-release injectable suspension within 5 minutes of shaking vigorously [see Dosage and Administration (2.8)].**

Paliperidone palmitate extended-release injectable suspension is intended for intramuscular use only. Do not administer by any other route. Avoid inadvertent injection into a blood vessel. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the deltoid or gluteal muscle.

Paliperidone palmitate extended-release injectable suspension must be administered using only the thin wall needles that are provided in the 3-month paliperidone palmitate extended-release injectable suspension pack. Do not use needles from the 1-month paliperidone palmitate extended-release injectable suspension pack or other commercially-available needles to reduce the risk of blockage.

#### **Deltoid Injection**

The recommended needle size for administration of paliperidone palmitate extended-release injectable suspension into the deltoid muscle is determined by the patient's weight:

- For patients weighing less than 90 kg, the 1-inch, 22 gauge thin wall needle is recommended.
- For patients weighing 90 kg or more, the 1½-inch, 22 gauge thin wall needle is recommended.

Administer into the center of the deltoid muscle. Deltoid injections should be alternated between the two deltoid muscles.

#### Gluteal Injection

Regardless of patient weight, the recommended needle size for administration of paliperidone palmitate extended-release injectable suspension into the gluteal muscle is the 1½-inch, 22 gauge thin wall needle. Administer into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be alternated between the two gluteal muscles.

#### Incomplete Administration

To avoid an incomplete administration of paliperidone palmitate extended-release injectable suspension, ensure that the prefilled syringe is **shaken vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension and ensure the needle does not get clogged during injection** [see *Dosage and Administration* (2.8)].

However, in the event of an incompletely administered dose, do **not** re-inject the dose remaining in the syringe and do **not** administer another dose of paliperidone palmitate extended-release injectable suspension. Closely monitor and treat the patient with oral supplementation as clinically appropriate until the next scheduled 3-month injection of paliperidone palmitate extended-release injectable suspension.

## 2.2 Schizophrenia

### Adults

3-month paliperidone palmitate extended-release injectable suspension is to be used only after 1-month paliperidone palmitate extended-release injectable suspension has been established as adequate treatment for at least four months. In order to establish a consistent maintenance dose, it is recommended that the last two doses of 1-month paliperidone palmitate extended-release injectable suspension be the same dosage strength before starting 3-month paliperidone palmitate extended-release injectable suspension.

Initiate 3-month paliperidone palmitate extended-release injectable suspension when the next 1-month paliperidone palmitate dose is scheduled with a 3-month paliperidone palmitate dose based on the previous 1-month injection dose, using the equivalent 3.5-fold higher dose as shown in Table 1. Paliperidone palmitate extended-release injectable suspension may be administered up to 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.



**Table 1. 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension Doses for Adult Patients Adequately Treated with 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension**

<b>If the Last Dose of 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension is:</b>	<b>Initiate 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension at the Following Dose:</b>
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the paliperidone palmitate extended-release injectable suspension 39 mg dose was not studied.

Following the initial paliperidone palmitate extended-release injectable suspension dose, paliperidone palmitate extended-release injectable suspension should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 273 mg to 819 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of paliperidone palmitate extended-release injectable suspension, the patient's response to an adjusted dose may not be apparent for several months [see *Clinical Pharmacology (12.3)*].

### 2.3 Missed Doses

#### Dosing Window

Missing doses of paliperidone palmitate extended-release injectable suspension should be avoided. If necessary, patients may be given the injection up to 2 weeks before or after the 3-month time point.

#### Missed Dose 3½ Months to 4 Months Since Last Injection

If more than 3½ months (up to but less than 4 months) have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, the previously administered paliperidone palmitate extended-release injectable suspension dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

#### Missed Dose 4 Months to 9 Months Since Last Injection

If 4 months up to and including 9 months have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, do NOT administer the next dose of paliperidone palmitate extended-release injectable suspension. Instead, use the re-initiation regimen shown in Table 2.

**Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of Paliperidone Palmitate Extended-Release Injectable Suspension**

If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension was:	Administer 1-month paliperidone palmitate extended-release injectable suspension, two doses one week apart (into deltoid muscle)		Then administer 3-month paliperidone palmitate extended-release injectable suspension (into deltoid <sup>a</sup> or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

<sup>a</sup> See Instructions for Use for deltoid injection needle selection based on body weight.

#### Missed Dose Longer than 9 Months Since Last Injection

If more than 9 months have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, re-initiate treatment with the 1-month paliperidone palmitate extended-release injectable suspension as described in the prescribing information for that product. 3-month paliperidone palmitate extended-release injectable suspension can then be resumed after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least 4 months.

#### 2.4 Use with Risperidone or with Oral Paliperidone

Since paliperidone is the major active metabolite of risperidone, caution should be exercised when paliperidone palmitate extended-release injectable suspension is coadministered with risperidone or oral paliperidone for extended periods of time. Safety data involving concomitant use of paliperidone palmitate extended-release injectable suspension with other antipsychotics is limited.

#### 2.5 Dosage Adjustment in Renal Impairment

Paliperidone palmitate extended-release injectable suspension has not been systematically studied in patients with renal impairment [see *Clinical Pharmacology* (12.3)]. For patients with mild renal impairment (creatinine clearance  $\geq 50$  mL/min to  $< 80$  mL/min [Cockcroft-Gault Formula]), adjust dosage and stabilize the patient using the 1-month paliperidone palmitate extended-release injectable suspension, then transition to 3-month paliperidone palmitate extended-release injectable suspension [see *Table 1, Dosage and Administration* (2.2)]. [See also *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)]

Paliperidone palmitate extended-release injectable suspension is not recommended in patients with moderate or severe renal impairment (creatinine clearance  $< 50$  mL/min) [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

819 mg	6 mg	9 mg	12 mg
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**2.8 Instructions for Use**

Administer every 3 months



Shake syringe vigorously for at least 15 seconds

**For intramuscular injection only. Do not** administer by any other route.**Important**

Paliperidone palmitate extended-release injectable suspension should be administered by a healthcare professional as a single injection. **DO NOT** divide dose into multiple injections.

Paliperidone palmitate extended-release injectable suspension is intended for intramuscular use only. Inject slowly, deep into the muscle taking care to avoid injection into a blood vessel.

Read complete instructions prior to use.

**Dosing**

This medication should be administered **once every 3 months**.

**Preparation**

Peel off tab label from the syringe and place in patient record.

3-month Paliperidone palmitate extended-release injectable suspension requires longer and more vigorous shaking than 1-month paliperidone palmitate extended-release injectable suspension. Shake the syringe vigorously, with the syringe tip pointing up, for **at least 15 seconds within 5 minutes prior to administration** (see Step 2).

**Thin Wall Safety Needle Selection**

Thin wall safety needles are designed to be used with paliperidone palmitate extended-release injectable suspension. Therefore, it is important to **only use the needles provided in the paliperidone palmitate extended-release injectable suspension kit**.



Manufactured for:  
**Mylan Institutional LLC**  
Morgantown, WV 26505 U.S.A.

Manufactured by:  
**Mylan Laboratories Limited**  
Bangalore, India

JUNE 2021

**PATIENT INFORMATION**  
**Paliperidone Palmitate**  
**(pal' ee per' i done pawl' mi tate)**  
**Extended-Release Injectable Suspension**

**What is the most important information I should know about paliperidone palmitate extended-release injectable suspension?**

**Paliperidone palmitate extended-release injectable suspension can cause serious side effects, including:**

- **Increased risk of death in elderly people who are confused, have memory loss and have lost touch with reality (dementia-related psychosis).** Paliperidone palmitate extended-release injectable suspension is not for treating dementia-related psychosis.

**What is paliperidone palmitate extended-release injectable suspension?**

Paliperidone palmitate extended-release injectable suspension is a prescription medicine given by injection by a healthcare professional and used to treat schizophrenia.

3-month paliperidone palmitate extended-release injectable suspension is used in people who have been treated with paliperidone palmitate extended-release injectable suspension 1 time a month injections for at least 4 months.

It is not known if paliperidone palmitate extended-release injectable suspension is safe and effective in children under 18 years of age.

**Who should not receive paliperidone palmitate extended-release injectable suspension?**

**Do not receive paliperidone palmitate extended-release injectable suspension if you:**

- are allergic to paliperidone palmitate, risperidone, or any of the ingredients in paliperidone palmitate extended-release injectable suspension. See the end of this Patient Information leaflet for a complete list of ingredients in paliperidone palmitate extended-release injectable suspension.

**What should I tell my healthcare provider before receiving paliperidone palmitate**

Page 50 of 54

**extended-release injectable suspension?**

Before you receive paliperidone palmitate extended-release injectable suspension, tell your healthcare provider about all your medical conditions, including if you:

- have had Neuroleptic Malignant Syndrome (NMS)
- have or have had heart problems, including a heart attack, heart failure, abnormal heart rhythm, or long QT syndrome
- have or have had low levels of potassium or magnesium in your blood
- have or have had uncontrolled movements of your tongue, face, mouth, or jaw (tardive dyskinesia)
- have or have had kidney or liver problems
- have diabetes or have a family history of diabetes
- have had a low white blood cell count
- have had problems with dizziness or fainting or are being treated for high blood pressure
- have or have had seizures or epilepsy
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if paliperidone palmitate extended-release injectable suspension will harm your unborn baby.
  - If you become pregnant while taking paliperidone palmitate extended-release injectable suspension, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or visit <http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/>.
  - Infants born to women who are treated with paliperidone palmitate extended-release injectable suspension may experience symptoms such as tremors, irritability, excessive sleepiness, eye twitching, muscle spasms, decreased appetite, difficulty breathing, or abnormal movement of arms and legs. Let your healthcare provider know if these symptoms occur.
- are breastfeeding or plan to breastfeed. Paliperidone palmitate extended-release injectable suspension can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive paliperidone palmitate extended-release injectable suspension.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

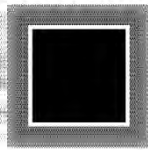
Know the medicines you take. Keep a list of them to show to your healthcare provider or pharmacist when you get a new medicine.

**How will I receive paliperidone palmitate extended-release injectable suspension?**

- Follow your paliperidone palmitate extended-release injectable suspension treatment schedule exactly as your healthcare provider tells you to.
- Your healthcare provider will tell you how much paliperidone palmitate extended-release injectable suspension you will receive and when you will receive it.
- Paliperidone palmitate extended-release injectable suspension is given as an injection by your

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# **THE JOURNAL OF CLINICAL PSYCHIATRY**

THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

## **SUPPLEMENT**

VOLUME 77 • 2016 • SUPPLEMENT 3  
SUPPLEMENT TO THE JOURNAL OF CLINICAL PSYCHIATRY

### **The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence**

Part 1: Efficacy and Safety of LAIs .....4

Part 2: Practical Considerations and  
Recommendations Regarding LAI Use.....16

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## The Use of Long-Acting Injectable Antipsychotics in Schizophrenia: Evaluating the Evidence

Christoph U. Correll, MD (Chair);

Leslie Citrome, MD, MPH; Peter M. Haddad, MD; John Lauriello, MD;

Mark Olfson, MD, MPH; Stephen M. Calloway; and John M. Kane, MD

Long-acting injectable antipsychotics (LAIs) are among the most effective treatments in psychiatry, yet they remain underutilized in clinical practice. Although LAIs are typically used to maintain treatment adherence in patients with chronic schizophrenia, recent research has suggested that they may also provide an effective treatment strategy for patients with early-phase or first-episode disease. In October 2015, a group of 8 experts on the management of schizophrenia and LAIs met to evaluate the evidence surrounding the efficacy, safety, and cost-effectiveness of LAIs and to develop practical recommendations regarding the clinical use, education, and unmet needs related to LAIs. Participants were also asked to rate the importance of several patient characteristics when choosing an LAI versus an oral antipsychotic, from the perspectives of 4 different stakeholder groups: patients, health care professionals, families, and payers. The evidence review demonstrated that LAIs are superior to placebo for acute and maintenance treatment of schizophrenia and, in general, appear to be similar to one another in terms of schizophrenia relapse prevention. Study design impacts the demonstrated efficacy of LAIs versus oral antipsychotics, but recent database and randomized controlled studies favor the use of LAIs in early-phase schizophrenia patients. LAIs vary considerably in their propensity to cause certain adverse effects, including weight gain, metabolic effects, extrapyramidal symptoms, and prolactin elevation, and these differences can be used to help guide LAI selection. Some studies, but not all, have demonstrated significant reductions in health care utilization or overall costs with LAIs. The expert panel identified several barriers to LAI use in current practice, including clinician lack of knowledge, negative attitudes about LAIs, and resource and cost issues. The participants also identified a number of additional factors that should be considered when weighing the use of LAI therapy, including medication adherence, relapse risk and severity, cognitive impairment, ease of use, substance misuse, access and cost, stigma, social support, patient autonomy, control over medication dosing, fear of needles, and the potential for patient harm due to relapses and associated loss of functioning. This evidence review, discussion, and summary recommendations may help clinicians, patients, families, payers, and other stakeholders to better characterize the role of LAIs in the treatment of schizophrenia.

(*J Clin Psychiatry* 2016;77[suppl 3]:1–24)  
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**G**iven the high frequency of suboptimal adherence to oral antipsychotics and the strong link between nonadherence and relapse, long-acting injectable antipsychotics (LAIs) are among the most effective treatments in psychiatry, yet they remain underutilized in clinical practice.<sup>1–4</sup> LAIs have traditionally been used in patients with chronic schizophrenia who have frequent relapses accompanied by marked social and occupational disabilities. However, it is likely that LAIs may benefit patients beyond the population of those with a history of poor treatment adherence. Recent research has focused in particular on the efficacy of LAIs in early-phase or first-episode schizophrenia. Although patients with a first episode of psychosis often respond very well to initial antipsychotic therapy, few are able to attain long-lasting symptom remission or functional recovery.<sup>5</sup> LAIs may provide an important treatment option for helping patients remain on therapy and reduce relapse risk and disease progression. As this supplement will demonstrate, LAIs may be underused for many reasons, including lack of familiarity among many physicians, inaccurate perceptions about safety and efficacy, cost and access to treatment, and negative perceptions of injectable therapy among patients, families, and providers.

This supplement was developed from a consensus roundtable that was held October 31, 2015. The goal of this roundtable was to examine current evidence regarding the role of LAIs in the treatment of schizophrenia in order to

develop specific, practical recommendations for their use in clinical practice. The panel also identified areas in which additional research is needed to better understand LAI use for schizophrenia as well as health care policy and education goals to improve appropriate implementation of LAIs.

### METHODS

A group of 8 experts on the management of schizophrenia and LAIs met to evaluate the evidence and to develop a set of recommendations regarding the clinical use, education, and unmet research needs related to LAIs. Attendees included representatives from academic and community psychiatry settings, the National Alliance on Mental Illness, and a commercial insurance company. Six attendees provided brief presentations related to LAIs, including efficacy, safety, considerations in clinical trial design, value and cost-effectiveness, patient selection, and optimizing LAI use. Participants discussed the information presented and used the information to develop recommendations for treatment, research, and policy.

Participants were also asked to rate the importance of several patient characteristics when choosing an LAI versus an oral antipsychotic. They rated the importance of each characteristic from the perspectives of 4 different stakeholder groups: patients, health care professionals, families, and payers. The importance of each characteristic and stakeholder group was

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**Table 4. Characteristics of Selected First-Generation and Second-Generation Long-Acting Injectable Antipsychotics (LAI) in the United States of America<sup>a</sup>**

Antipsychotic	Base	Dose Interval	Dosage Strengths/Forms	Starting Dose	Maintenance Dose	Oral Supplementation	Time to Peak	Steady State	Postinjection Observation
Fluphenazine decanoate <sup>61</sup>	Oil	Varies	25 and 100 mg/mL ampoules/vials/syringes	Varies, 12.5 mg	Varies, 12.5–100 mg	No	2–4 d	2–3 mo	No
Haloperidol decanoate <sup>62</sup> (Haldol and others)	Oil	4 wk	50 and 100 mg/mL ampoules	Varies, 50 mg	Varies, 300 mg	No	6–7 d	2–3 mo	No
Risperidone microspheres <sup>63</sup> (Risperdal Consta)	Water	2 wk	25, 37.5, 50 mg vial kits	25 mg	25 mg (25–50 mg)	3 wk	4–6 wk	1.5–2 mo	No
Olanzapine pamoate <sup>64</sup> (Zyprexa Relprevv)	Water	2 or 4 wk	210, 300, 405 mg vial kits	Varies, up to 300 mg/2 wk	Varies, up to 300 mg/2 wk	No	4 d	3 mo	At least 3 hours
Paliperidone palmitate LAI <sup>65</sup> (Invega Sustenna)	Water	Monthly	78, 117, 156, 234 mg prefilled syringes	150 mg (day 1) + 100 mg (day 8)	75 mg (25–150 mg)	No	13 d	7–11 mo	No
Paliperidone palmitate LAI <sup>66</sup> (Invega Trinza)	Water	Once every 3 mo	273, 410, 546, 819 mg prefilled syringes	Depending on once-monthly dose	Varies, 273–819 mg	No	30–33 d	Continues steady state at equivalent dose	No
Aripiprazole monohydrate <sup>67</sup> (Abilify Maintena)	Water	Monthly	300, 400 mg vial kits and dual-chamber syringe	400 mg	400 mg (300–400 mg)	2 wk	5–7 d	400: 4–8 mo; 300: 3–4 mo	No
Aripiprazole lauroxil <sup>68</sup> (Aristada)	Water	Monthly (or 6 weekly: 882 mg)	441, 662, 882 mg prefilled syringes	Varies, 441–882 mg	Varies, 441–882 mg	3 wk	4 d	4–6 mo	No

<sup>a</sup>Data from package inserts of each antipsychotic and Citrome.<sup>10</sup>

side effects including sedation, extrapyramidal symptoms (EPSs), weight gain, metabolic disturbance, and prolactin elevation.<sup>90</sup> However, a simple division of FGAs and SGAs in terms of side effect profiles is today generally seen as simplistic and misleading, although in the past it was advocated. Adverse events (AEs) may contribute to poor treatment adherence and increased long-term morbidity, and they may limit the maximal level of functional recovery that patients can achieve.<sup>91,92</sup> Importantly, patients and physicians may differ in their perceptions of the importance of AEs. The roundtable participants felt that patients are more likely to respond to the subjective distress produced by side effects, whereas clinicians typically focus more on the objective severity of the AE and how this affects patient safety and risk. All of these issues should be addressed through shared decision-making and psychoeducational approach.<sup>93</sup>

**Comparison of adverse events associated with antipsychotic drugs.** AEs associated with LAIs generally follow the known AE profiles of the oral molecule. In a large meta-analysis of 15 antipsychotics in schizophrenia, antipsychotics were ranked by 5 different AE domains (sedation, EPSs, weight gain, prolactin elevation, and QTc elevation). Results indicated small to large differences in adverse events among antipsychotics<sup>90</sup> that should be taken into consideration also when choosing among LAIs. A more recent meta-analysis of 16 RCTs (n = 4,902) showed that of 119 reported adverse events, LAIs and oral antipsychotics did not differ significantly, aside from akinesia, low-density lipoprotein cholesterol change, anxiety (higher with LAIs), and prolactin change (lower with LAIs).<sup>93a</sup>

Differences in AE rates between antipsychotic drugs may be quantified using number needed to harm (NNH). NNH answers the question “How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional outcome of interest that you would like to avoid?” In general, NNH values < 10 for medication versus placebo denote potentially common AEs that can be expected to be seen frequently in day-to-day clinical practice.<sup>94–96</sup> As shown in Supplementary eTable 2, NNH versus placebo can help to determine how often we can expect to encounter important adverse outcomes such as weight gain ≥ 7%, somnolence, or akathisia with different atypical antipsychotics.<sup>97,98</sup>

Overall, treatment discontinuation rates have generally been similar for patients treated with LAI antipsychotics versus the same oral agent.<sup>99</sup> The most common AEs with LAIs are summarized in Supplementary eTable 3.<sup>82–88</sup>

**Considerations in choosing an LAI.** Practical issues that can help in selecting among LAIs are summarized in Table 5.<sup>97</sup>

**Summary and conclusions.** Information about adverse event differences among LAIs comes largely from indirect comparisons and spontaneously reported AEs. The available data suggest that LAIs vary considerably in their propensity to cause certain adverse effects, including weight gain, EPSs, and prolactin elevation. This information can be used to help guide the selection of LAIs.

#### Implications of Study Design

LAIs have been examined using several study design strategies—RCTs, mirror-image studies, and cohort studies—each of which has strengths and limitations.<sup>18,73,77</sup>



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Table 5. Considerations in Selection of a Long-Acting Injectable Antipsychotic

Consideration	Selecting a Long-Acting Injectable Antipsychotic (LAI)
Is the patient demonstrating adequate efficacy and tolerability on oral fluphenazine, haloperidol, risperidone, paliperidone, olanzapine, or aripiprazole?	<ul style="list-style-type: none"> <li>Switching to the corresponding LAI formulation is relatively simple</li> <li>For patients receiving oral risperidone, paliperidone palmitate may be considered for convenience</li> <li>For patients receiving oral fluphenazine or haloperidol, potential disadvantages should be weighted for using concomitant oral anticholinergic agents for the management of motor adverse effects, which adds complexity to the regimen and may interfere with memory and other cognitive functions</li> </ul>
Is the patient being treated acutely, and is the patient averse to using oral medications?	<ul style="list-style-type: none"> <li>Consider LAI antipsychotics that do not require oral supplementation, where the clinical trials have demonstrated acute efficacy (either paliperidone palmitate or olanzapine pamoate)</li> </ul>
Are weight gain and metabolic adverse effects a concern for this individual patient?	<ul style="list-style-type: none"> <li>Consider aripiprazole LAI, paliperidone palmitate, or risperidone microspheres among the second-generation antipsychotics, in that order</li> <li>A first-generation LAI antipsychotic may also be considered in this case</li> </ul>
Is prolactin elevation a clinical concern for this individual patient?	<ul style="list-style-type: none"> <li>Consider aripiprazole LAI</li> <li>Avoid paliperidone palmitate, risperidone microspheres, or first-generation LAI antipsychotics</li> </ul>
Is cost the primary concern?	<ul style="list-style-type: none"> <li>First-generation LAI antipsychotics may be the only option</li> </ul>
Are any of the following people or entities not enrolled in the Olanzapine Pamoate Patient Care Program: patient, prescriber, health care facility, pharmacy?	<ul style="list-style-type: none"> <li>Olanzapine pamoate cannot be used</li> </ul>

RCTs are usually considered the “gold standard” for comparing the efficacy and safety of different treatments. However, explanatory RCTs are most likely not the optimal study design for the comparison of LAIs with oral antipsychotics. Strengths of RCTs include objective rating of patient outcomes and the elimination of biases on the part of investigators, including expectations about the different treatments. However, this approach may not be the best way to study interventions with potential adherence benefits, as patients enrolled in RCTs may differ from the general patient population in important ways, including higher levels of motivation or willingness to comply with instructions. RCT patients may also have less severe disease than many of those seen in typical practice. In addition, the trial itself, with reminders for appointments, more comprehensive assessments, payments for participation, free medication, and so on, can impact adherence rates.

Mirror-image studies examine patients who are switched from one medication to another, comparing pretreatment with posttreatment study periods. This design is more reflective of actual clinical practice than an RCT. Expectation bias is inherent in the design of a mirror-image study and may affect the main outcome. In mirror-image studies of LAIs, patients have been switched from oral antipsychotics to LAIs, but no studies have examined reversing this switching sequence. This design is also subject to potential time or cohort effects (eg, changing hospitalization practices over time).

In cohort studies, patient selection bias is reduced compared with other study types. However, the selection of medication in open studies may introduce bias by improving adherence. More importantly, patients selected for treatment with LAIs in cohort studies may be categorically different than those treated with oral antipsychotics, including having greater severity of illness and less illness insight or psychosocial support. Therefore, it is important to identify and adjust for confounding factors. One analysis of outcomes from LAI studies found that as study designs shift toward real-world

patient populations, LAIs are associated with a larger magnitude of improvement on outcomes, such as relapses, hospitalizations, and all-cause discontinuation.<sup>100</sup>

**Summary and conclusions.** LAIs have been studied in RCTs, mirror-image studies, and cohort studies, each of which has its own strengths and limitations. Therefore, different methodological issues must be considered in the design and interpretation of clinical studies examining the effects of LAIs, creating a full picture only when viewed from these different angles.

#### Effect of LAIs on Adherence and Costs

**Medication nonadherence in schizophrenia.** Studies have demonstrated that approximately one-third of patients with schizophrenia are poorly adherent to oral medications at any time, whether this is evaluated using reports from patients, family members, other caregivers, or clinicians.<sup>101–104</sup> More importantly, nonadherence is even higher when patients are followed over time. For example, in a study<sup>105</sup> of more than 34,000 patients with schizophrenia in the Veterans Health Administration, approximately one-third were nonadherent in any one year, but more than 60% of patients were nonadherent at some point during the 4-year study, where nonadherence was defined as an entire year with a medication possession ratio <0.8. Consistent nonadherence across all 4 years of the study was noted for 18% of the patients. This suggests that medication adherence is suboptimal but also varies over the long-term treatment course. Detection of nonadherence in clinical practice is often challenging, and adherence assessed by patient self-report or physician judgment may be markedly lower than adherence measured using quantitative techniques, such as pill counting, pharmacy records, or blood antipsychotic level tests.<sup>106</sup> Potential clinical consequences of undetected medication nonadherence include unnecessary antipsychotic medication or dosage changes, addition of concomitant medications, and labeling

of patients as "treatment resistant."<sup>106,107</sup> A 3-year, prospective study<sup>108</sup> that examined functional outcomes associated with treatment adherence in patients with schizophrenia found that nonadherent patients had higher rates of several adverse outcomes, including psychiatric hospitalization (26.8% vs 14.1% for nonadherent vs adherent patients, respectively), emergency care (10% vs 6%), arrest (8.4% vs 3.5%), violent behaviors (10.8% vs 4.8%), being the victim of a crime (15.1% vs 7.8%), and substance misuse (31.1% vs 21.5%).<sup>108</sup>

Poor treatment adherence is usually considered the primary clinical indication for LAI use, yet studies have reported that fewer than 20% of patients with schizophrenia receive LAIs, even when there is evidence of recent poor treatment adherence.<sup>40,109</sup>

**Health care costs.** Studies have examined how the use of LAIs affects overall health care cost of patients with schizophrenia. One study<sup>110</sup> compared treatment costs for patients with schizophrenia or schizoaffective disorder who were randomized to either risperidone LAI (n=187) or the physician's choice of an oral antipsychotic (n=182). Overall, mean quarterly outpatient medication costs were higher for patients randomized to LAI (\$3,028) than oral medication (\$1,913;  $P=.003$ ), although total treatment costs did not differ significantly between the two treatments (\$14,916 vs \$13,980;  $P=.73$ ). Health care utilization and costs have also been compared among propensity score-matched adults with schizophrenia in the Veterans Health Administration system who initiated use of either LAI or oral antipsychotics. During the 12-month follow-up period, patients treated with LAI compared to oral antipsychotics had significantly lower average inpatient costs, higher average pharmacy costs, and similar total health care costs.<sup>111</sup>

A recent Medicaid health care utilization study<sup>112</sup> in the United States compared health care utilization and treatment costs for hospitalized patients with schizophrenia who had been on short-duration LAI treatment (defined as 30–79 days; n=2,856) versus longer-term LAI treatment ( $\geq 180$  days; n=2,838). The longer-term LAI patients had significantly lower levels of some health care utilization measures, including mean number of hospitalizations and mean length of hospital stay. Mean total hospital payments were 26% lower for patients in the long-term LAI group than those in the short-term LAI group, suggesting that the economic benefit of LAI therapy may increase over time. Lin and colleagues<sup>113</sup> compared real-world health care costs and medication adherence between patients with schizophrenia who initiated LAI (n=394) versus oral antipsychotics (n=2,610) using medical claims data from commercially insured patients. Schizophrenia-related hospital costs decreased by a mean of \$5,981 in the LAI group and increased by a mean of \$758 for patients who received oral antipsychotics ( $P<.001$ ). Mean outpatient cost increased by \$134 versus \$568 for the LAI and oral antipsychotic groups, respectively ( $P=.023$ ). The mean drug cost was \$4,132 with LAIs versus \$2,562 with oral agents ( $P<.001$ ). Similar outcomes were observed in patients with Medicare coverage.

The impact of LAI use on health care costs has also been examined in several international studies. A mirror-image

study conducted in Taiwan<sup>114</sup> examined treatment costs from medical claims data during 1 year before and after initiating LAI therapy. After a switch from oral to LAI antipsychotics, mean costs decreased for some outcomes (eg, inpatient services, other nonmedication services) but increased for others (eg, outpatient psychiatry, medication costs). A mirror-image study performed with patients treated in public hospitals in Hong Kong<sup>114</sup> found that switching from oral to LAI therapy was associated with significantly lower total medical costs driven largely by lower hospitalization costs, although outpatient department and pharmacy costs significantly increased during the LAI treatment period. By contrast, a mirror-image study conducted in the United Kingdom,<sup>115</sup> which included predominantly patients with schizophrenia, reported that in the year following LAI therapy initiation, total health care costs significantly increased along with inpatient bed days, although the number of inpatient admissions declined. These unexpected results may be partially explained by the high level of illness severity reflected in the large proportion of study patients who started LAI therapy as inpatients. In a study conducted in Sweden,<sup>116</sup> investigators modeled per-patient costs associated with several sequences of LAI or oral antipsychotics, including total costs associated with medical care, institutional care, and indirect costs. Treatment strategies that used LAIs had lower total 1-year treatment costs than strategies that included oral antipsychotic therapy. A strategy of paliperidone palmitate LAI followed by olanzapine LAI for patients with relapses was considered not only cost-effective but also cost-saving for the health care system as a whole, compared with other antipsychotic strategies.

A prospective observational study<sup>117</sup> that recruited and followed adults with schizophrenia from 10 European countries provides additional support for health care savings related to LAI therapy. Among outpatients who were previously medication nonadherent, those who initiated FGA LAIs were significantly more likely to be medication adherent (55%) than those who initiated FGA oral agents (39%) during the 18-month follow-up period. The total schizophrenia-related treatment costs of the patients treated with LAIs were only one-half of those incurred by the patients treated with oral antipsychotics. Finally, a study conducted in Canada<sup>118</sup> compared health care resource use during 1 year before and after initiation of LAI treatment in 1,992 patients with schizophrenia or schizoaffective disorder. Overall 1-year costs associated with health care utilization were significantly lower after a switch to LAI therapy (\$27,234 vs \$16,987 for the preinitiation vs the postinitiation year;  $P<.001$ ).

**Summary and conclusions.** Nonadherence in patients with schizophrenia is common and difficult to detect. Although LAIs may provide one method to help improve treatment adherence, only a minority of medication nonadherent patients receive them. Significant reductions in health care utilization or costs associated with schizophrenia have been demonstrated in some studies of LAI antipsychotics, although other studies have not demonstrated these effects and showed cost-neutrality or even greater cost.

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**PART 2: PRACTICAL CONSIDERATIONS AND RECOMMENDATIONS REGARDING LAI USE****When to Consider LAI Treatment:****Patient Eligibility and Selection**

**Guidelines for LAI use.** Several schizophrenia management guidelines, including those by the American Psychiatric Association, recognize LAIs as a treatment option but usually only when nonadherence to oral medication has resulted in repeated schizophrenia relapses or when LAI is preferred by the patient.<sup>119–122</sup> However, even when guidelines recommend LAIs as an option if preferred by the patient, many patients may not be aware that LAIs are available.

**Patient and mental health provider perceptions of LAIs.**

The use of LAIs in clinical practice may depend to a large degree on provider and patient attitudes, which are closely related to previous and current experiences. In a survey of attitudes about LAIs among patients with schizophrenia shortly before hospital discharge, acceptance of LAI therapy was 73% among patients who were current users of LAIs ( $n=60$ ), 45% among past users of LAIs ( $n=95$ ), and 23% among LAI-naïve patients ( $n=145$ ).<sup>123</sup> These data show that patients are more likely to favor their current treatment. Similar findings were reported in a study of outpatients with schizophrenia or schizoaffective disorder in the United Kingdom.<sup>124</sup> Perceptions about LAI use may also differ among health care providers. In a survey in the United Kingdom,<sup>125</sup> most psychiatrists (91%) felt that LAIs were as efficacious as oral medications and improve patient adherence (81%) and prevent relapse (94%); however, despite this, 48% felt that depot medications are stigmatizing, and 69% believed LAI antipsychotics are less acceptable to patients. However, psychiatrists' knowledge about LAIs was positively associated with more favorable attitudes ( $r=0.39$ ,  $P<.001$ ). When these data were compared to data from a survey of nurses in the United Kingdom, the nurses were significantly more likely than the psychiatrists to characterize LAIs as coercive, compromising of patient autonomy, or more bothersome to prescribe and monitor than oral medication.<sup>126</sup>

**Why are psychiatrists reluctant to use LAIs?** Despite the high rate of nonadherence and the consequences of poor adherence among patients with schizophrenia, many psychiatrists remain reluctant to use LAI antipsychotics. Most psychiatrists say that they are interested in using LAI antipsychotics only if they can be clearly shown to be superior to oral agents. For example, in a survey of 106 German psychiatrists, most favored an LAI only if it was associated with an absolute decrease in relapse rate of 10% compared with oral therapy.<sup>127</sup>

In addition, many clinicians lack knowledge about practical issues in the use of LAIs, including dose selection, pharmacokinetics, and what to do when a patient is late for an injection or has persistent symptoms after starting therapy. Younger staff members may have little or no experience with FGA LAIs. Many clinicians mistakenly believe that LAIs are associated with a greater side effect burden than oral agents, among other misconceptions about LAI treatment. Clinician attitudes may also be a barrier to LAI use. Physicians

often overestimate the treatment adherence of their own patients, and they may have concerns about suggesting LAIs to their patients because of beliefs about stigmatization or coercion.<sup>125,128</sup>

Although several studies suggested possible benefits of LAIs in first-episode schizophrenia,<sup>43,74,75</sup> surveys of clinicians have shown that many psychiatrists regard LAIs as inappropriate for first-episode patients.<sup>128,129</sup> In a study conducted in the United Kingdom, approximately one-third of psychiatrists thought that LAIs were always inappropriate for first-episode patients, whereas in a German study approximately 70% of psychiatrists thought that LAIs were inappropriate for a first episode.<sup>128,129</sup> In many cases, physician beliefs and perceptions about LAIs may prevent patients from learning that LAIs are a potential option.<sup>130,131</sup> For example, in a study of communication patterns in the offer of LAIs made by psychiatrists to patients with schizophrenia at 10 health clinics, psychiatrists generally presented LAIs in a negative light, resulting in only 11 of 33 LAI recommendations (33%) being accepted by patients.<sup>132</sup> However, during a postvisit interview, during which LAIs were presented in a more positive light and with more information, 27 of the 28 patients (96%) who declined the initial recommendation changed their mind, stating that they actually would be willing to try LAI treatment.

Other obstacles to LAI use include service barriers (eg, lack of community nurses to administer injections, failure to consider partnering with primary care providers to administer maintenance LAI treatment) and financial barriers (eg, higher acquisition costs, payer reluctance to cover LAIs unless there is clear documentation of nonadherence, clinician and payer failure to consider the total costs associated with treating the illness).<sup>123,125</sup>

**What patient and illness factors should influence LAI use?** Several factors may favor the use of LAI therapy in patients with schizophrenia:

- Willingness by clinicians to consider LAI treatment
- Early-phase or first-episode schizophrenia, as these patients usually have the most to gain by remaining in remission and the most to lose through relapse (eg, in terms of education or employment)
- A history of nonadherence with oral medication
- Risk factors that are associated with increased risk of poor adherence, such as younger age, comorbid substance misuse, or lack of insight
- Factors that suggest a high risk of relapse and that relapse is associated with significant clinical risk, such as a history of psychosis associated with vulnerability, self-harm, or aggression or a history of violence
- Preference of LAI by the patient

Conversely, LAIs may be less suitable for some patients, including those who demonstrate intolerance to or inefficacy

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with the parent compound, establish good adherence with oral therapy, have a strong preference for oral therapy, or require chronic anticoagulation therapy. Furthermore, cost considerations may limit access to LAIs in certain states or settings.

**What factors should influence LAI selection?** As the efficacy of different LAIs is generally similar, side effect profiles are often a key consideration when selecting an LAI. However, few studies have directly compared side effect profiles of different LAIs in the treatment of schizophrenia. Rubio and colleagues<sup>133</sup> compared risperidone LAI and zuclopenthixol decanoate in patients with schizophrenia and substance misuse. Over 6 months of follow-up, risperidone LAI was associated with fewer EPSs as well as more improvement on the Positive and Negative Syndrome Scale and better adherence to a substance use management plan. McEvoy and colleagues<sup>78</sup> compared haloperidol LAI and paliperidone LAI in patients with schizophrenia, reporting greater weight gain and prolactin elevation but less akathisia with paliperidone LAI, although changes in glucose and lipid parameters and in the overall rate of EPS were similar between the two treatment groups. Finally, Naber and colleagues<sup>80</sup> examined use of aripiprazole LAI and paliperidone LAI in patients with schizophrenia, reporting that aripiprazole LAI was associated with numerically fewer adverse events and treatment discontinuations and significantly greater improvement in interviewer-rated quality of life scores.

In the absence of an extensive body of research comparing the safety profiles of different LAIs, it is reasonable to extrapolate from the oral formulation of the same drug. Meta-analysis has quantified the relative risk of a range of side effects using data from RCTs of oral antipsychotics.<sup>90</sup> Cost is often an important consideration in treatment selection, with acquisition costs of SGA LAIs higher than those of FGA LAIs. Finally, the patient's current oral regimen is also an important consideration. If the patient is well stabilized on one oral medication, switching to a different medication in a LAI formulation might be associated with a risk of relapse or new adverse effects. In such cases, there would be an argument for using the same antipsychotic in LAI form, assuming this was available.

**Summary and conclusions.** Schizophrenia treatment guidelines generally emphasize nonadherence and relapse with oral antipsychotic agents as the most important reasons for LAI use. Barriers to LAI use in current practice include clinicians' lack of knowledge and negative attitudes about LAIs, resource issues, and cost. Those who might benefit from LAIs include first-episode patients and patients early in the course of psychosis as well as patients with known poor adherence, high risk of nonadherence, lack of insight, and the potential for significant consequences associated with relapse.

#### Best Practices to Maximize LAI Acceptability and Experience for Stakeholders

The appropriate use of antipsychotics is a concern not only for patients and physicians but also for many additional stakeholder groups, including family and friends, employers,

court-appointed guardians, law enforcement and the judiciary, and society as a whole. In some cases, stakeholder groups may have differing interests and concerns. For example, in a survey of perceptions about medication use, patients with schizophrenia were less likely to agree that the good things about medication outweigh the bad (61% of patients) than were psychiatrists (81%) or family members (80%).<sup>130</sup> Stakeholder groups may also differ in their attitudes toward other issues, such as medication cost, access to care, and reimbursement.

**Patient-centered medicine.** The concept of patient-centered medicine provides one approach that can help optimize LAI treatment and find a balance between the concerns and considerations of patients and physicians. Patient-centered medicine seeks to focus attention first on the needs and concerns of the patient, rather than the physician, and to consider social and economic factors.<sup>134</sup> Several steps may help to maximize alignment of treatment goals between patient and provider. The clinician should take a thorough history and listen carefully to the patient's account and beliefs. The patient should be given time to make his or her views known and to ask questions. Consideration of the patient's past positive and negative treatment experiences is critical to developing a successful treatment plan. The clinician should be flexible, adjusting treatment when appropriate to make sure the patient has a voice in his or her care. However, the clinician should not agree to a treatment plan that is not clinically indicated or that could result in patient harm. Patient-centered care relies heavily on collaboration between the provider, the patient, the patient's family members, and other caregivers as well as a broader support network, such as close friends or clergy. Patients should be encouraged to be involved in all aspects of planning, delivery, and evaluation of their health services, with particular emphasis on empowering patients and family members to make effective decisions.<sup>135</sup>

**Education.** Psychoeducation for patients about schizophrenia and the benefits and risks of its treatment is clearly a critical part of this process and may be especially important in making decisions about the use of LAIs. Psychoeducation should also reinforce the concept that the patient is "an expert" by experience and that the patient should be involved in the development of the treatment plan. Education should also include a plan to improve adherence, crisis management, and prevention of relapses and suicide.

Likewise, education about the potential benefits of LAIs should also be provided to clinicians and the health care team.<sup>136</sup> Health care providers should be able to anticipate and address issues that patients have about LAIs. The first step in this educational process is to acknowledge concerns about using LAIs. An overview of the benefits and limitations of LAIs should be followed by detailed education about LAI therapy and its most appropriate uses. Team members are often the first line of contact to identify patients for whom LAIs may improve outcomes and to educate those patients and their families about this treatment option.

There is also a need to educate clinicians regarding practical issues associated with the dosing and switching of LAIs

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use INVEGA® SUSTENNA® safely and effectively. See full prescribing information for INVEGA® SUSTENNA®.

INVEGA® SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use  
Initial U.S. Approval: 2006

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. (5.1)
- INVEGA® SUSTENNA® is not approved for use in patients with dementia-related psychosis. (5.1)

**RECENT MAJOR CHANGES**

Indications and Usage, Schizoaffective Disorder (1.2) 11/2014

**INDICATIONS AND USAGE**

INVEGA® SUSTENNA® is an atypical antipsychotic indicated for

- Treatment of schizophrenia. (1.1)
- Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants. (1.2)

**DOSAGE AND ADMINISTRATION**

- For intramuscular injection only. (2.1)
- Each injection must be administered only by a health care professional. (2.1)
- For deltoid injection, use 1-inch 23G needle for patients weighing less than 90 kg or 1½-inch 22G needle for patients weighing 90 kg or more. For gluteal injection, use 1½-inch 22G needle regardless of patient weight. (2.1)

Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose* (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia (2.2)	234 mg	156 mg	39-234 mg <sup>b</sup>	234 mg
Schizoaffective disorder (2.2)	234 mg	156 mg	78-234 mg <sup>c</sup>	234 mg

\* Administered 5 weeks after the first injection.

<sup>b</sup> The recommended maintenance dose for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).

<sup>c</sup> Adjust dose based on tolerability and/or efficacy using available strengths. The 39 mg strength was not studied in the long-term schizoaffective disorder study.

- For patients naïve to oral paliperidone or oral or injectable risperidone, establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA®. (2.2)
- Missed Doses: To manage either a missed second initiation dose or a missed monthly maintenance dose, refer to the Full Prescribing Information. (2.3)
- Moderate to severe renal impairment (creatinine clearance < 50 mL/min): INVEGA® SUSTENNA® is not recommended. (2.5)
- Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Administer 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Follow with monthly injections of 78 mg in either the deltoid or gluteal muscle. (2.5)

**DOSAGE FORMS AND STRENGTHS**

Extended-release injectable suspension: 39 mg, 78 mg, 117 mg, 156 mg, or 234 mg (3)

**CONTRAINDICATIONS**

Known hypersensitivity to paliperidone, risperidone, or to any excipients in the formulation (4)

**WARNINGS AND PRECAUTIONS**

- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:** Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). INVEGA® SUSTENNA® is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation of drug and close monitoring (5.3)
- QT Prolongation:** Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)
- Tardive Dyskinesia:** Discontinue drug if clinically appropriate (5.5)
- Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
  - Hyperglycemia and Diabetes Mellitus:** Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
  - Dyslipidemia:** Undesirable alterations have been observed. (5.6)
  - Weight Gain:** Significant weight gain has been reported. Monitor weight gain. (5.6)
- Orthostatic Hypotension and Syncope:** Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis:** Monitor complete blood count in patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.8)
- Hyperprolactinemia:** Prolactin elevations occur and persist during chronic administration (5.9)
- Potential for Cognitive and Motor Impairment:** Use caution when operating machinery (5.10)
- Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.11)

**ADVERSE REACTIONS**

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

**DRUG INTERACTIONS**

- Drugs that may cause orthostatic hypotension: An additive effect may occur when co-administered with INVEGA® SUSTENNA®. (7.1)
- Strong CYP3A4/P-glycoprotein (P-gp) inducers: It may be necessary to increase the dose of INVEGA® SUSTENNA® when a strong inducer of both CYP3A4 and P-gp (e.g., carbamazepine, rifampin, St John's wort) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of INVEGA® SUSTENNA®. (7.2, 12.3)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy:** Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers:** Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2014

PTX-106

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## 2.2 Schizophrenia and Schizoaffective Disorder

For patients who have never taken oral paliperidone or oral or injectable risperidone, it is recommended to establish tolerability with oral paliperidone or oral risperidone prior to initiating treatment with INVEGA® SUSTENNA®.

The recommended dosing of INVEGA® SUSTENNA® for each approved indication is displayed in Table 1. The recommended initiation of INVEGA® SUSTENNA® is with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

**Table 1. Recommended Dosing of INVEGA® SUSTENNA® for Adults with Schizophrenia or Schizoaffective Disorder**

Indication	Initiation Dosing (deltoid)		Monthly Maintenance Dose <sup>a</sup> (deltoid or gluteal)	Maximum Monthly Dose
	Day 1	Day 8		
Schizophrenia	234 mg	156 mg	39-234 mg <sup>b</sup>	234 mg
Schizoaffective disorder	234 mg	156 mg	78-234 mg <sup>c</sup>	234 mg

<sup>a</sup> Administered 5 weeks after the first injection.

<sup>b</sup> The recommended maintenance dose for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).

<sup>c</sup> Adjust dose based on tolerability and/or efficacy using available strengths. The 39 mg strength was not studied in the long-term schizoaffective disorder study.

Adjustment of the maintenance dose may be made monthly. When making dose adjustments, the prolonged-release characteristics of INVEGA® SUSTENNA® should be considered [*see Clinical Pharmacology (12.3)*], as the full effect of the dose adjustment may not be evident for several months.

## 2.3 Missed Doses

### Avoiding Missed Doses

It is recommended that the second initiation dose of INVEGA® SUSTENNA® be given one week after the first dose. To avoid a missed dose, patients may be given the second dose 4 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

**PTX-106**

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Reference ID: 3657038

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**Management of a Missed Second Initiation Dose**

If the target date for the second INVEGA® SUSTENNA® injection (one week  $\pm$  4 days) is missed, the recommended reinitiation depends on the length of time which has elapsed since the patient's first injection. In case of a missed second initiation dose follow the dosing instructions provided in Table 2.

**Table 2. Management of a Missed Second Initiation Dose.**

<b>TIMING OF MISSED SECOND INITIATION DOSE</b>	<b>DOSING</b>
<b>Less than 4 weeks since first injection</b>	<p>Administer the second initiation dose of 156 mg in the deltoid muscle as soon as possible.</p> <ol style="list-style-type: none"> <li>1. It is recommended to administer a third injection of 117 mg in either the deltoid or gluteal muscle 5 weeks after the first injection (regardless of the timing of the second injection).</li> <li>2. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.</li> </ol>
<b>4 to 7 weeks since first injection</b>	<p>Resume dosing with two injections of 156 mg in the following manner:</p> <ol style="list-style-type: none"> <li>1. Administer a deltoid injection as soon as possible.</li> <li>2. Administer a second deltoid injection 1 week later.</li> <li>3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.</li> </ol>
<b>More than 7 weeks since first injection</b>	<p>Restart dosing with recommended initiation (see Section 2.2, Table 1):</p> <ol style="list-style-type: none"> <li>1. Administer a 234 mg deltoid injection on Day 1.</li> <li>2. Administer a 156 mg deltoid injection 1 week later.</li> <li>3. Thereafter, resume regular monthly dosing in either the deltoid or gluteal muscle.</li> </ol>

**Management of a Missed Maintenance Dose**

In case of a missed maintenance dose follow the dosing instructions provided in Table 3.

**Table 3. Management of a Missed Maintenance Dose.**

<b>TIMING OF MISSED MAINTENANCE DOSE</b>	<b>DOSING</b>
<b>4 to 6 weeks since last injection</b>	<p>Resume regular monthly dosing as soon as possible at the patient's previously stabilized dose, followed by injections at monthly intervals.</p>
<b>More than 6 weeks to 6 months since last injection</b>	<p>Resume the same dose the patient was previously stabilized on (unless the patient was stabilized on a dose of 234 mg, then the first 2 injections should each be 156 mg) in the following manner:</p> <ol style="list-style-type: none"> <li>1. Administer a deltoid injection as soon as possible.</li> </ol>

**PTX-106**



	<ol style="list-style-type: none"> <li>Administer a second deltoid injection 1 week later at the same dose.</li> <li>Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.</li> </ol>
More than 6 months since last injection	<p><b>Restart dosing with recommended initiation</b> (<i>see Section 2.2, Table 1</i>):</p> <ol style="list-style-type: none"> <li>Administer a 234 mg deltoid injection on Day 1.</li> <li>Administer a 156 mg deltoid injection 1 week later.</li> <li>Thereafter, resume administering the previously stabilized dose in the deltoid or gluteal muscle 1 month after the second injection.</li> </ol>

#### 2.4 Use with Oral Paliperidone or with Risperidone

Concomitant use of INVEGA® SUSTENNA® with oral paliperidone or oral or injectable risperidone has not been studied. Since paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if any of these medications are coadministered with INVEGA® SUSTENNA®.

#### 2.5 Dosage Adjustments

##### Renal Impairment

INVEGA® SUSTENNA® has not been systematically studied in patients with renal impairment [*see Clinical Pharmacology (12.3)*]. For patients with mild renal impairment (creatinine clearance  $\geq 50$  mL/min to  $< 80$  mL/min [Cockcroft-Gault Formula]), initiate INVEGA® SUSTENNA® with a dose of 156 mg on treatment day 1 and 117 mg one week later. Administer both doses in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

INVEGA® SUSTENNA® is not recommended in patients with moderate or severe renal impairment (creatinine clearance  $< 50$  mL/min) [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

##### Coadministration with Strong CYP3A4/P-glycoprotein (P-gp) Inducers

It may be necessary to increase the dose of INVEGA® SUSTENNA® when a strong inducer of both CYP3A4 and P-gp (e.g., carbamazepine, rifampin, St John's wort) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of INVEGA® SUSTENNA® [*see Drug Interactions (7.2) and Clinical Pharmacology (12.3)*].

**PTX-106**

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Following administration of paliperidone palmitate the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.6–1.8.

Based on a population analysis, the apparent volume of distribution of paliperidone is 391 L. The plasma protein binding of racemic paliperidone is 74%.

#### Metabolism and Elimination

In a study with oral immediate-release  $^{14}\text{C}$ -paliperidone, one week following administration of a single oral dose of 1 mg immediate-release  $^{14}\text{C}$ -paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates.

The median apparent half-life of paliperidone following INVEGA® SUSTENNA® single-dose administration over the dose range of 39 mg - 234 mg ranged from 25 days - 49 days.

#### Long-Acting Paliperidone Palmitate Injection versus Oral Extended-Release Paliperidone

INVEGA® SUSTENNA® is designed to deliver paliperidone over a monthly period while extended-release oral paliperidone is administered on a daily basis. The initiation regimen for INVEGA® SUSTENNA® (234 mg/156 mg in the deltoid muscle on Day 1/Day 8) was designed to rapidly attain steady-state paliperidone concentrations when initiating therapy without the use of oral supplementation.

In general, overall initiation plasma levels with INVEGA® SUSTENNA® were within the exposure range observed with 6-12 mg extended-release oral paliperidone. The use of the INVEGA® SUSTENNA® initiation regimen allowed patients to stay in this exposure window of 6-12 mg extended-release oral paliperidone even on trough pre-dose days (Day 8 and Day 36). The intersubject variability for paliperidone pharmacokinetics following delivery from INVEGA® SUSTENNA® was lower relative to the variability determined from extended-release oral paliperidone tablets. Because of the difference in median pharmacokinetic profiles between the two products, caution should be exercised when making a direct comparison of their pharmacokinetic properties.

**PTX-106**

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Reference ID: 3657038

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**Table 13. Schizophrenia Short-term Studies**

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference <sup>a</sup> (95% CI)
Study 1	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (39 mg/4 weeks)*	86.9 (11.99)	-11.2 (1.69)	-5.1 (-9.01, -1.10)
	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (156 mg/4 weeks)*	86.2 (10.77)	-14.8 (1.68)	-8.7 (-12.62, -4.78)
	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (234 mg/4 weeks)*	88.4 (11.70)	-15.9 (1.70)	-9.8 (-13.71, -5.85)
	Placebo	86.8 (10.31)	-6.1 (1.69)	--
Study 2 <sup>b</sup>	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (78 mg/4 weeks)	89.9 (10.78)	-6.9 (2.50)	-3.5 (-8.73, 1.77)
	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (156 mg/4 weeks)*	90.1 (11.66)	-10.4 (2.47)	-6.9 (-12.12, -1.68)
	Placebo	92.4 (12.55)	-3.5 (2.15)	--
Study 3	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (39 mg/4 weeks)*	90.7 (12.25)	-19.8 (2.19)	-6.6 (-11.40, -1.73)
	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (78 mg/4 weeks)*	91.2 (12.02)	-19.2 (2.19)	-5.9 (-10.76, -1.07)
	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (156 mg/4 weeks)*	90.8 (11.70)	-22.5 (2.18)	-9.2 (-14.07, -4.43)
	Placebo	90.7 (12.22)	-13.3 (2.21)	--
Study 4	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (78 mg/4 weeks)*	88.0 (12.39)	-4.6 (2.43)	-11.2 (-16.85, -5.57)
	INVEGA <sup>®</sup> SUSTENNA <sup>®</sup> (156 mg/4 weeks)*	85.2 (11.09)	-7.4 (2.45)	-14.0 (-19.51, -8.58)
	Placebo	87.8 (13.90)	6.6 (2.45)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

<sup>a</sup> Difference (drug minus placebo) in least-squares mean change from baseline.<sup>b</sup> Because an insufficient number of subjects received the 234 mg/4 weeks dose, results from this group are not included.

\* p&lt;0.05 (Doses statistically significantly superior to placebo).

**Maintenance Monotherapy Treatment (Study 5: PSY-3001)**

The efficacy of INVEGA<sup>®</sup> SUSTENNA<sup>®</sup> in maintaining symptomatic control in schizophrenia was established in a longer-term double-blind, placebo-controlled, flexible-dose study involving adult subjects who met DSM-IV criteria for schizophrenia. This study included a minimum 12-week, fixed-dose stabilization phase, and a randomized, placebo-controlled phase to observe for relapse. During the double-blind phase, patients were randomized to either the same dose of INVEGA<sup>®</sup> SUSTENNA<sup>®</sup> they received during the stabilization phase, i.e., 39 mg, 78 mg, or 156 mg administered every 4 weeks, or to placebo. A total of 410 stabilized patients were randomized to either INVEGA<sup>®</sup> SUSTENNA<sup>®</sup> or to placebo until they experienced a relapse of schizophrenia symptoms. Relapse was pre-defined as time to first emergence of one or more of the following: psychiatric hospitalization,  $\geq 25\%$  increase (if the baseline score was  $> 40$ ) or a 10-point increase (if the baseline score was  $\leq 40$ ) in total PANSS score on two consecutive

**PTX-106**

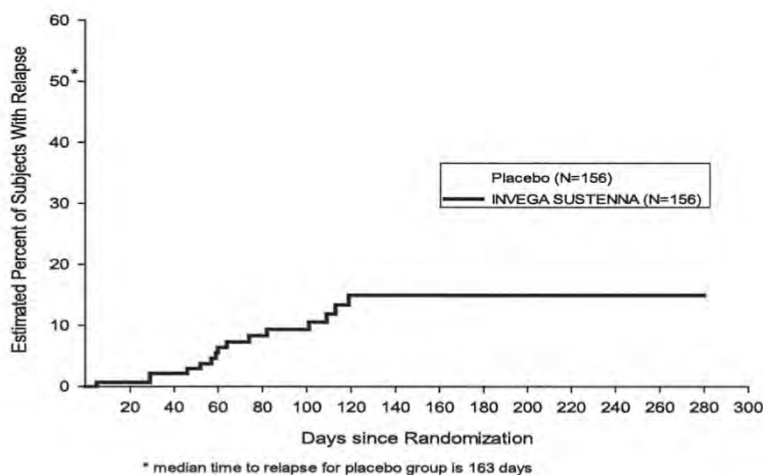
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assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of  $\geq 5$  (if the maximum baseline score was  $\leq 3$ ) or  $\geq 6$  (if the maximum baseline score was 4) on two consecutive assessments of the specific PANSS items. The primary efficacy variable was time to relapse. A pre-planned interim analysis showed a statistically significantly longer time to relapse in patients treated with INVEGA® SUSTENNA® compared to placebo, and the study was stopped early because maintenance of efficacy was demonstrated. Thirty-four percent (34%) of subjects in the placebo group and 10% of subjects in the INVEGA® SUSTENNA® group experienced a relapse event. There was a statistically significant difference between the treatment groups in favor of INVEGA® SUSTENNA®. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 1. The time to relapse for subjects in the placebo group was statistically significantly shorter than for the INVEGA® SUSTENNA® group. An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

**Figure 1:** Kaplan-Meier Plot of Cumulative Proportion of Subjects with Relapse Over Time (Schizophrenia Study 5)



**PTX-106**

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## Research

## Original Investigation

# Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial

Joris Berwaerts, MD; Yanning Liu, MS; Srihari Gopal, MD, MHS; Isaac Nuamah, PhD; Haiyan Xu, PhD; Adam Savitz, MD, PhD; Danielle Coppola, MD; Alain Schotte, PhD; Bart Remmerie, Chem Eng; Nataliya Maruta, MD, PhD; David W. Hough, MD

**IMPORTANCE** Treatment nonadherence and relapse are common problems in patients with schizophrenia. The long-acting 3-month formulation of paliperidone palmitate, owing to its extended elimination half-life, may offer a valuable therapeutic option for these patients.

**OBJECTIVE** To evaluate the efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo in delaying time to relapse of schizophrenia symptoms.

**DESIGN, SETTING, AND PARTICIPANTS** This randomized, multicenter trial conducted from April 26, 2012, through April 9, 2014, in 8 countries consisted of 4 phases: 3-week screening phase, flexible-dose 17-week open-label transition phase, 12-week open-label maintenance phase, and open-ended double-blind (DB) phase. Of the 506 patients enrolled (aged 18-70 years; DSM-IV-TR diagnosis of schizophrenia), 305 were randomized to 3-month paliperidone palmitate (n = 160) or placebo (n = 145) in the DB phase.

**INTERVENTIONS** Patients received once-monthly doses of the 1-month formulation of paliperidone palmitate (50, 75, 100, or 150 mg eq) during the transition phase, followed by a single dose of the 3-month formulation (3.5 times the stabilized dose of once-monthly paliperidone palmitate) during the maintenance phase. Stabilized patients were randomized to receive either a fixed dose of 3-month paliperidone palmitate (175, 263, 350, or 525 mg eq) or placebo once every 3 months during the DB phase.

**MAIN OUTCOMES AND MEASURES** Time from randomization to the first relapse event (time to relapse) in the DB phase.

**RESULTS** In the interim analysis, time to first relapse was significantly different in favor of the paliperidone palmitate group vs the placebo group (hazard ratio = 3.45; 95% CI, 1.73-6.88;  $P < .001$ ); median time to relapse was 274 days for placebo but not estimable for 3-month paliperidone palmitate. An independent data monitoring committee recommended early study termination due to efficacy. In the DB phase, 183 of 305 patients (62% with 3-month paliperidone palmitate; 58% with placebo) had at least 1 treatment-emergent adverse event; those noted more frequently in the group receiving paliperidone palmitate than in the placebo group were headache (9% vs 4%), weight increased (9% vs 3%), nasopharyngitis (6% vs 1%), and akathisia (4% vs 1%).

**CONCLUSIONS AND RELEVANCE** Compared with placebo, the 3-month formulation of paliperidone palmitate administered 4 times yearly significantly delayed time to relapse in patients with schizophrenia. The 3-month formulation was generally tolerable and has a safety profile consistent with other marketed paliperidone formulations.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT01529515

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← Editorial page 745

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**R**elapse of schizophrenia symptoms, which can result from poor adherence to otherwise effective antipsychotic therapy, may lead to treatment resistance, cognitive impairment, personal distress, and interference with rehabilitation efforts.<sup>1,2</sup> Each episode of worsening symptoms presents with a risk of hospitalization, imposing significant burden on health care resources.<sup>3-6</sup> Patients with schizophrenia commonly lack insight into their disease and the importance of medication, compromising treatment adherence and increasing relapse frequency. Long-acting injectable (LAI) antipsychotics eliminate the need for daily dosing, thus circumventing the problem of nonadherence with antipsychotic medications and reducing the risk of relapse and hospitalization due to nonadherence among patients with schizophrenia.<sup>7,8</sup>

Paliperidone palmitate was originally formulated as a once-monthly atypical antipsychotic LAI and is approved for treatment of schizophrenia in adults in numerous countries.<sup>9-11</sup> The acute and sustained efficacy and tolerability profile of once-monthly paliperidone palmitate has been shown in more than 3800 patients.<sup>11-22</sup> Continued treatment with once-monthly paliperidone palmitate in patients who initially responded to it for acute worsening of symptoms resulted in a nearly 4-fold reduction in relapse risk compared with patients randomized to placebo.<sup>16</sup> A recently developed 3-month formulation offers a substantially longer dosing interval: injections are administered once every 3 months. This extended dosing interval offers the prospect of fewer opportunities for nonadherence than currently available LAI formulations, thus reducing relapse risk as a result of subtherapeutic plasma concentrations and its associated negative consequences in patients with schizophrenia.<sup>2,23,24</sup>

This double-blind (DB), placebo-controlled, relapse prevention study was designed to evaluate the efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo in delaying time to relapse of schizophrenia symptoms in patients previously treated with once-monthly paliperidone palmitate for at least 4 months.

## Methods

### Patients

Patients (men and women aged 18-70 years, inclusive) diagnosed with schizophrenia (by *DSM-IV-TR* criteria) for at least 1 year before screening and a Positive and Negative Syndrome Scale (PANSS) total score lower than 120 at screening and baseline were enrolled (Figure 1). Patients symptomatically stable on other LAI antipsychotic treatments were eligible. A stable place of residence for the previous 3 months before screening was mandatory. During initiation of the study and at subsequent times, the investigators were instructed to seek authorization from medical monitors if they elected to keep individual patients in the hospital for longer than 10 consecutive days after enrollment in the study. The medical monitors ensured that patients did not remain in the hospital, if clinically stable, beyond the second injection of once-monthly paliperidone palmitate on day 8 of the open-label (OL) transition phase. Patients were not to enter the OL maintenance phase and re-

ceive an injection of the 3-month formulation of paliperidone palmitate if still hospitalized at that time, ie, for a total of 17 weeks of OL treatment with once-monthly paliperidone palmitate, regardless of their clinical presentation. Patients were allowed assistance from an identified support person to ensure compliance with study treatment and procedures, including alerting trial staff to any signs of impending relapse. Major exclusion criteria were the following: primary, active *DSM-IV* diagnosis other than schizophrenia; significant risk of suicidal behavior; history of substance dependence within 6 months before screening; involuntary status in a psychiatric hospital at screening; or history of neuroleptic malignant syndrome, tardive dyskinesia, or any malignant neoplasm in the previous 5 years except basal cell carcinoma.

The study protocol and amendments were approved by an independent ethics committee or institutional review board, as appropriate, for each site. All studies were conducted in compliance with the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. Written informed consent was obtained from all patients before enrollment. The trial protocol is available in Supplement 1.

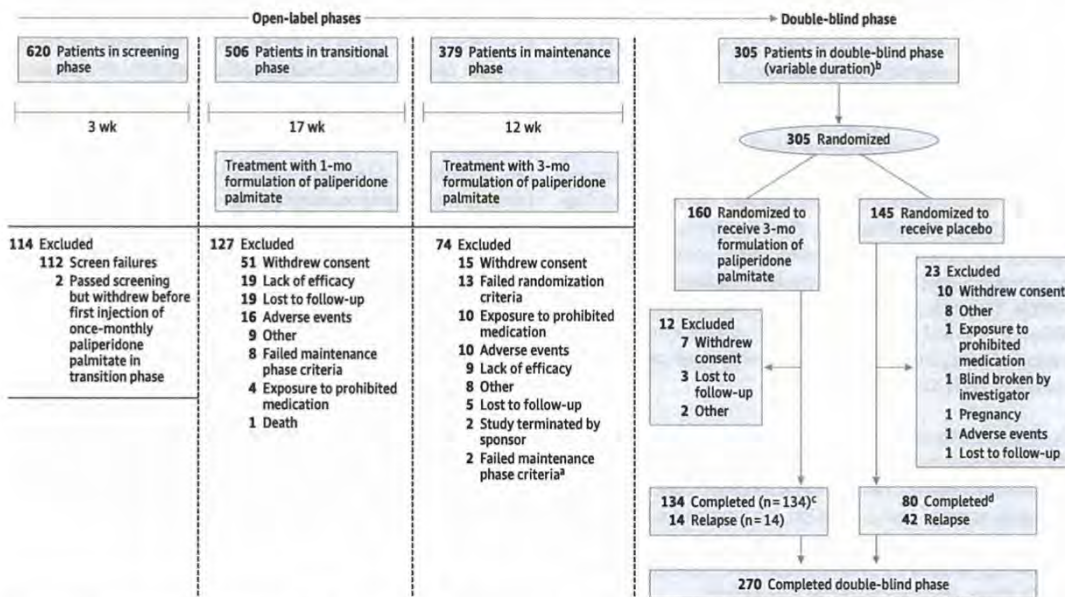
### Study Design, Randomization, and Blinding

This randomized, DB, placebo-controlled study conducted from April 26, 2012, through April 9, 2014, included patients from 64 centers in 8 countries (Ukraine [36%], United States [31%], Romania [8%], Colombia [8%], Malaysia [6%], Mexico [6%], Turkey [3%], and South Korea [2%]). Investigators from all centers participated in the study (eAppendix 1 in Supplement 2). The study consisted of 4 phases: screening and oral tolerability testing phase ( $\leq 3$  weeks), OL transition phase, OL maintenance phase, and DB phase. In the 17-week transition phase, all patients except those switching from other LAI antipsychotics or those who were receiving once-monthly paliperidone palmitate before study entry received once-monthly paliperidone palmitate for 120 days, with the following doses: day 1: 150 mg eq (deltoid); day 8: 100 mg eq (deltoid); days 36 and 64: 50, 75, 100, or 150 mg eq flexible doses (deltoid or gluteal); and day 92: same dose of once-monthly paliperidone palmitate as on day 64. At the start of the 12-week maintenance phase, patients received a single dose of 3-month paliperidone palmitate in either the deltoid or gluteal muscle (dose of 3-month paliperidone palmitate was 3.5-fold that of the final once-monthly paliperidone palmitate dose administered on day 92).

Stabilized patients were then randomized (1:1 ratio; via a sponsor-prepared computer-generated randomization scheme; administered by an interactive voice/web response system) to receive either 3-month paliperidone palmitate or placebo in a DB phase with variable length (fixed dose of 3-month paliperidone palmitate). The doses of 3-month paliperidone palmitate were 175, 263, 350, or 525 mg eq. Patients assigned to 3-month paliperidone palmitate in the DB phase received the same dose that was administered on day 120 of the maintenance phase; this dose remained fixed throughout the DB phase (eTable 1 in Supplement 2). Randomization was balanced using permuted blocks across the 2 treatment groups and stratified by study center to ensure balance of treatment allocation within a center. To maintain blinding during the DB phase, paliperi-



Figure 1. CONSORT Flow Diagram of Study Design



<sup>a</sup> Two patients failed to meet criteria to enter the maintenance phase but continued into the maintenance phase by mistake and received an injection of the 3-month formulation of paliperidone palmitate at visit 8. These 2 patients withdrew from the maintenance phase because they did not meet criteria to enter the maintenance phase.

<sup>b</sup> Duration of the double-blind phase was variable, with the patients continuing until they experienced a relapse event and completed all end-of-study assessments; met 1 or more of the study discontinuation or withdrawal criteria; or had remained relapse free during the double-blind phase until the

study was terminated for efficacy at the interim analysis (occurrence of 42 relapse events) or because of 70 relapse events being recorded.

<sup>c</sup> The duration of exposure to the 3-month formulation of paliperidone palmitate (maintenance and double-blind phases) ranged from 16 to 540 days; the median treatment duration in the double-blind phase was 169 days.

<sup>d</sup> The median duration of receiving placebo in the double-blind phase was 146 days.

done palmitate and placebo were wrapped so the content was not visible and were administered by a single person distinct from other study personnel at the investigational site. The patient was not allowed to view the syringe. The placebo (Intralipid, 20%) had a similar appearance to the 1-month and 3-month formulations of paliperidone palmitate. The study drug administrator was appropriately medically trained to administer an intramuscular medication and was the only person responsible for drug accountability, receiving interactive voice/web response system information and medication allocation. Patients remained in the DB phase until they relapsed, they withdrew from the study, or the study was terminated.

Doses of paliperidone palmitate can be expressed both in terms of milligram equivalent of the pharmacologically active fraction, paliperidone, and in milligrams of paliperidone palmitate. Thus, the doses expressed as 25, 50, 75, 100, and 150 mg eq of once-monthly paliperidone palmitate equate to 39, 78, 117, 156, and 234 mg, respectively, of once-monthly paliperidone palmitate. Similarly, 175, 263, 350, and 525 mg eq of 3-month paliperidone palmitate correspond to 273, 410, 546, and 819 mg of 3-month paliperidone palmitate (eTable 2 in Supplement 2).

An independent data monitoring committee performed ongoing safety monitoring and 1 efficacy interim analysis and provided recommendations about modifying, stopping, or continuing the study. The independent data monitoring committee consisted of 4 academic psychiatrists and 1 statistician who independently reviewed safety data on a periodic (quarterly) basis and performed 1 planned unblinded efficacy analysis. The protocol planned for an interim analysis after 42 relapse events and full analysis after 70 relapse events had occurred if the study was not terminated at the interim efficacy analysis. On recommendation to terminate the study based on interim results, all ongoing patients were brought in for end-of-study evaluation. Results through the end of the DB phase after early termination of the study (ie, cumulative data including those from before the interim cutoff date) are reported herein as the final analysis, which confirmed the results of the interim analysis.

#### Efficacy Assessments

The primary efficacy variable was time from randomization to the first relapse event in the DB phase. Relapse was based on the definition by Csernansky et al<sup>25</sup> and defined as at least 1 of the following: (1) hospitalization for schizophrenia symptoms (involuntary or voluntary admission); (2) 25% increase in PANSS total



score from randomization for 2 consecutive assessments between 3 and 7 days apart for patients scoring higher than 40 at randomization or a 10-point increase for patients scoring 40 or lower at randomization; (3) increase in distinct PANSS item scores (P1 [delusions], P2 [conceptual disorganization], P3 [hallucinatory behavior], P6 [suspiciousness/persecution], P7 [hostility], or G8 [uncooperativeness]) for 2 consecutive assessments between 3 and 7 days apart; (4) clinically significant deliberate self-injury or violent behavior resulting in suicide, injury, or significant damage; or (5) suicidal or homicidal ideation and aggressive behavior. The relapse criteria were identical to those implemented in the relapse prevention studies of extended-release paliperidone<sup>26</sup> and once-monthly paliperidone palmitate<sup>16</sup> in patients with schizophrenia. Secondary efficacy end points included changes from DB baseline to end point in PANSS total, subscale, and 5-factor scores,<sup>27</sup> Clinical Global Impression–Severity score, and Personal and Social Performance scores.

### Pharmacokinetic and Safety Assessments

The pharmacokinetic assessments are described in eAppendix 2 in Supplement 2. Safety assessments included treatment-emergent adverse events (TEAEs), extrapyramidal symptom (EPS) rating scales, clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms, physical examination findings, and injection-site evaluations.

### Statistical Analysis

The sample size determination is described in eAppendix 2 in Supplement 2.

The Kaplan-Meier method was used to assess the primary efficacy variable (time to relapse), and the log-rank test (2-sided) was used to compare treatment differences. Treatment comparison between 3-month paliperidone palmitate and placebo in changes from baseline to end point of PANSS total, subscale, and 5-factor scores, Personal and Social Performance scores, and Clinical Global Impression–Severity score during the DB phase was performed using an analysis-of-covariance model with treatment and country as factors and DB baseline value as a covariate. All secondary efficacy analyses were performed at the significance level of  $\alpha = .05$  (2-sided) across treatment groups with no adjustments for multiplicity. Cox proportional hazards models were constructed to individually examine the effect of covariates (age, sex, race, body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], and geographic region) on the primary efficacy results. Least-squares estimates of the treatment differences and 95% confidence intervals were calculated.

The study was to be stopped if efficacy was established (at a 2-sided significance level of  $\alpha = .0101$ ) at the preplanned interim analysis (after 42 relapse events). If the study was not terminated due to nonsignificant results, the final analysis (after 70 relapse events) was to be performed at a significance level of  $\alpha = .0464$  (2-sided).

## Results

Of the 506 patients enrolled, 305 (60%) were randomized to either 3-month paliperidone palmitate ( $n = 160$ ) or placebo

( $n = 145$ ) in the DB phase. Of 305 randomized patients, a total of 270 (89%) completed the study (Figure 1). The median treatment duration was 120 days for the transition phase, 85 days for the maintenance phase, and 169 days for the group receiving 3-month paliperidone palmitate and 146 days for the placebo group in the DB phase. Demographic and baseline characteristics were well balanced between the groups (Table 1). The most common reason for discontinuation from this study was consent withdrawal. A total of 11 (2%), 42 (8%), 241 (48%), and 212 (42%) of the patients received the final dose of 50, 75, 100, and 150 mg eq of once-monthly paliperidone palmitate, respectively, in the transition phase, while 9 (2%), 36 (9%), 185 (49%), and 149 (39%) of the patients received 175, 263, 350, and 525 mg eq of 3-month paliperidone palmitate, respectively, at week 17 in the maintenance phase. Of these, 6 (4%) of the patients receiving 175 mg eq, 15 (9%) receiving 263 mg eq, 78 (49%) receiving 350 mg eq, and 61 (38%) receiving 525 mg eq entered the DB phase. A greater proportion of patients who entered the DB phase receiving 525 mg eq of 3-month paliperidone palmitate (14 of 61 patients [23%]) continued in the study to DB week 36 vs other dose groups (175 mg eq: 0 of 6 patients; 350 mg eq: 8 of 78 patients [10%]; 263 mg eq: 3 of 15 patients [20%]).

### Efficacy

#### Primary

The interim analysis (considered the primary analysis) was conducted on data collected from April 26, 2012, through data cutoff on January 24, 2014. The analysis set (DB) for the interim analysis included 283 patients (3-month paliperidone palmitate,  $n = 148$ ; placebo,  $n = 135$ ). The interim analysis revealed a significant difference between the 2 treatment groups for time to relapse of schizophrenia symptoms, in favor of 3-month paliperidone palmitate (hazard ratio = 3.45; 95% CI, 1.73–6.88;  $P < .001$ ); the median time to relapse was 274 days for the placebo group but was not estimable for the group receiving 3-month paliperidone palmitate (Figure 2A). Based on the interim analysis, 31 patients (23%) in the placebo group and 11 patients (7%) in the group receiving 3-month paliperidone palmitate experienced a relapse event during the DB phase (eTable 3 in Supplement 2). Consequently, the independent data monitoring committee recommended early study termination for efficacy.

The final analysis set (DB) included 305 patients (3-month paliperidone palmitate:  $n = 160$ ; placebo:  $n = 145$ ). Final analysis results were consistent with that of interim analysis, confirming superiority of 3-month paliperidone palmitate over placebo for delaying time to relapse of schizophrenia symptoms ( $P < .001$ ; hazard ratio = 3.81; 95% CI, 2.08–6.99); the median time to relapse was 395 days for the placebo group but was not estimable for the group receiving 3-month paliperidone palmitate (Figure 2B). A total of 42 patients (29%) in the placebo group and 14 patients (9%) in the group receiving 3-month paliperidone palmitate experienced a relapse event during the DB phase (eTable 3 in Supplement 2). Additionally, based on Cox proportional hazards model, the efficacy of 3-month paliperidone palmitate with regard to time to relapse was consistent regardless of age, sex, race, BMI, or region ( $P < .001$  for all, regardless of which factor is included in the model) (eTable 4 and eTable 5 in Supplement 2).



**Table 1. Demographic and Baseline Characteristics in the Double-Blind Phase for the Intent-to-Treat Analysis Set**

Characteristic	Placebo (n = 145)	3-mo Paliperidone Palmitate (n = 160)	Total (n = 305)
Age, mean (SD), y	38.5 (11.16)	37.1 (10.87)	37.8 (11.01)
Male, No. (%)	110 (76)	118 (74)	228 (75)
Race, No. (%)			
White	91 (63)	104 (65)	195 (64)
Black or African American	21 (14)	24 (15)	45 (15)
Asian	15 (10)	14 (9)	29 (10)
Other	18 (12)	17 (11)	35 (11)
Multiple	0	1 (1)	1 (<1)
Weight, mean (SD), kg	77.1 (15.53)	78.1 (14.97)	77.6 (15.22)
BMI, mean (SD)	26.2 (4.57)	26.2 (4.51)	26.2 (4.53)
Age at schizophrenia diagnosis, mean (SD), y	27.7 (8.98)	26.3 (8.24)	26.9 (8.61)
Use of depot antipsychotics prior to study start, No. (%)			
Yes	25 (17)	28 (18)	53 (17)
No	120 (83)	132 (83)	252 (83)
No. of prior hospitalizations, No. (%) <sup>a</sup>			
0	51 (40)	48 (33)	99 (36)
1	44 (34)	48 (33)	92 (34)
2	18 (14)	25 (17)	43 (16)
3	7 (5)	14 (10)	21 (8)
≥4	8 (6)	11 (8)	19 (7)
Score at double-blind phase baseline, mean (SD) <sup>b</sup>			
PANSS	54.2 (9.34)	54.9 (9.95)	54.5 (9.66)
CGI-S	2.8 (0.65)	2.7 (0.67)	2.7 (0.66)
PSP	68.6 (9.01)	68.8 (9.27)	68.7 (9.14)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CGI-S, Clinical Global Impression-Severity; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance.

<sup>a</sup> Number of prior hospitalizations for psychosis within 24 months before study start.

<sup>b</sup> Scores on the PANSS range from 30 to 210, with higher scores indicating more symptoms; CGI-S scores range from 1 to 7, with higher scores indicating a more severe overall clinical condition; and PSP scores range from 1 to 100, with higher scores indicating better functioning.

## Secondary

The mean (SD) PANSS total score at DB baseline was 54.9 (9.95) for patients randomized to 3-month paliperidone palmitate and 54.2 (9.34) for those randomized to placebo. The mean PANSS total score remained stable during the DB phase for patients receiving 3-month paliperidone palmitate but increased in the placebo group, with a significant difference in change from the DB baseline (mean [SD] change,  $-0.5$  [8.36] vs  $6.7$  [14.40], respectively;  $P < .001$ ; least-squares means difference,  $-7.2$ ; 95% CI,  $-9.87$  to  $-4.60$ ) (Figure 3). There were also significant differences ( $P \leq .005$ ) in mean change from DB baseline to end point between the group receiving 3-month paliperidone palmitate and the placebo group for PANSS subscale and Marder factor scores (except negative subscale and negative symptoms factor), Clinical Global Impression-Severity score (mean [SD] change,  $0.1$  [0.60] vs  $0.4$  [0.87], respectively;  $P < .001$ ; least-squares means difference,  $-0.3$ ; 95% CI,  $-0.50$  to  $-0.18$ ), and Personal and Social Performance scores (mean [SD] change,  $-0.5$  [6.63] vs  $-4.2$  [9.70], respectively;  $P < .001$ ; least-squares means difference,  $3.8$ ; 95% CI,  $1.89$  to  $5.65$ ) (eTable 6 and eTable 7 in Supplement 2). Change in remitter status (eTable 8 in Supplement 2) supports maintenance of efficacy in the DB phase for those continuing treatment with 3-month paliperidone palmitate compared with those randomized to placebo.

## Pharmacokinetics and Safety

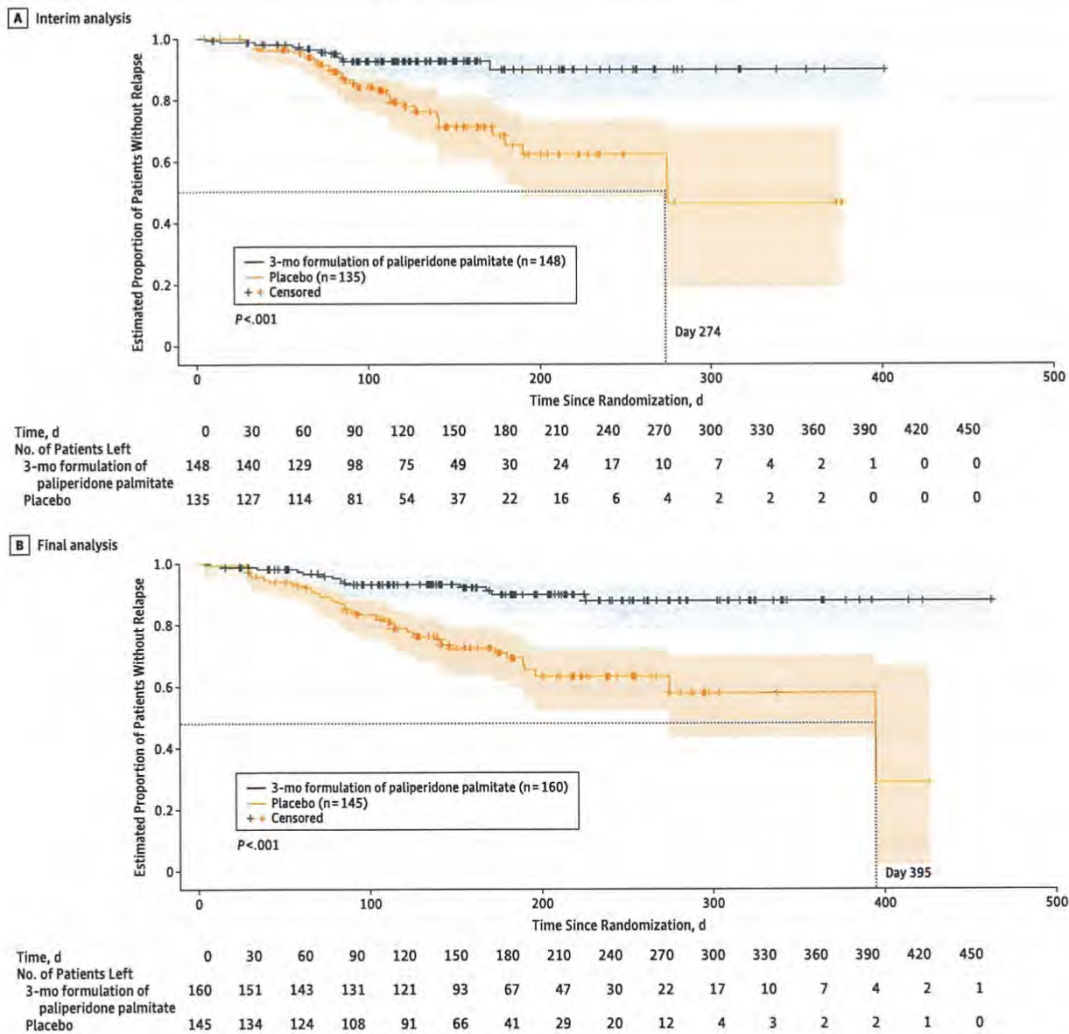
The results for pharmacokinetics are described in eAppendix 3 and the eFigure in Supplement 2.

Regarding safety, a total of 330 of 506 patients (65%) in the OL phase and 183 of 305 patients (60%) in the DB phase (62% of those receiving 3-month paliperidone palmitate vs 58% of those receiving placebo) had at least 1 TEAE. The most frequently reported TEAEs ( $\geq 2\%$ ) in the group receiving 3-month paliperidone palmitate during the maintenance phase were anxiety (6%), insomnia (5%), weight increased (4%), and headache (3%) (eTable 9 in Supplement 2). During the maintenance phase, the TEAEs that led to study discontinuation in more than 1 patient included psychiatric disorders (3 [1%]) and schizophrenia (2 [0.5%]). The most commonly occurring EPS-related TEAEs ( $\geq 1\%$ ) were those grouped under hyperkinesia (6 [2%]) and parkinsonism (5 [1%]). One patient (0.3%) experienced a hyperglycemia-related TEAE of type 2 diabetes mellitus during the maintenance phase.

During the DB phase, the most common TEAEs occurring more frequently in the group receiving 3-month paliperidone palmitate than in the placebo group were headache (9% vs 4%, respectively), weight increased (9% vs 3%, respectively), nasopharyngitis (6% vs 1%, respectively), and EPS-related TEAEs (8% vs 3%, respectively [akathisia, 4% vs 1%, respectively]). The placebo group compared with the group receiving



Figure 2. Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase



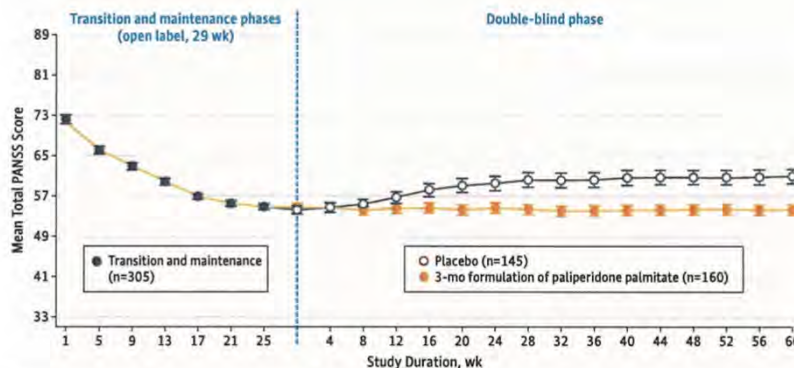
The median time to relapse indicates the time (in days) since randomization at which the cumulative survival function equals 0.5. Shaded areas indicate 95% confidence interval for the estimated proportion of patients who remained in the study without relapse at distinct times after randomization in the double-blind phase. A, Interim analysis. The median time to relapse was 274 days for placebo and was not estimable for the 3-month formulation of paliperidone palmitate. B, Final analysis. The median time to relapse was 395 days for placebo and was not estimable for 3-month paliperidone palmitate. Of

the 160 patients randomized to 3-month paliperidone palmitate in the double-blind phase (175 mg eq: 6 patients [4%]; 263 mg eq: 15 patients [9%]; 350 mg eq: 78 patients [49%]; and 525 mg eq: 61 patients [38%]), a total of 25 patients (16%) continued at week 36. A greater proportion of patients receiving 525 mg eq of 3-month paliperidone palmitate (14 of 61 patients [23%]) continued in the study to double-blind phase week 36 vs other dose groups (175 mg eq: 0 of 6 patients; 350 mg eq: 8 of 78 patients [10%]; 263 mg eq: 3 of 15 patients [20%]).

3-month paliperidone palmitate more commonly had anxiety (11% vs 8%, respectively), insomnia (12% vs 7%, respectively), and weight decreased (8% vs 1%, respectively) (Table 2). A higher percentage of patients who received placebo (8 of 145 [6%]) vs those treated with 3-month paliperidone palmitate (4 of 160 [3%]) experienced glucose-related TEAEs. One of 145 patients (1%) in the placebo group and 15 of 160 patients (10%)

in the group receiving 3-month paliperidone palmitate experienced a clinically significant increase in body weight ( $\geq 7\%$ ) from DB baseline to end point. Six patients (4%) in the group receiving 3-month paliperidone palmitate reported injection site-related TEAEs, of which injection site pain was most frequently reported (2 patients [1%]). Prolactin-related TEAEs (amenorrhea) occurred in 1 of 42 women (2%) in the group

Figure 3. Positive and Negative Syndrome Scale (PANSS) Total Scores Over Time



Error bars indicate standard error.

treated with 3-month paliperidone palmitate. A higher percentage of patients who received placebo than those treated with 3-month paliperidone palmitate experienced a treatment-emergent abnormally high heart rate relative to the predose average (10 of 141 [7%] vs 3 of 155 [2%], respectively). Serious TEAEs occurred 4 times more often in the placebo group than in the group receiving 3-month paliperidone palmitate (10% vs 3%, respectively) and were mostly related to increase in psychiatric symptoms. Only 1 TEAE (increased transaminase levels, in the placebo group) led to treatment discontinuation during the DB phase. No deaths were reported during the DB phase; 1 death (in a patient treated with once-monthly paliperidone palmitate) was reported during the OL phase due to a TEAE of megacolon, which was considered not related to the study agent by the investigator. Additional details are included in eTables 9 to 16 in Supplement 2.

## Discussion

Relapse episodes culminating in diminished functioning, homelessness, incarceration, and increased societal costs<sup>3-5</sup> are common downstream outcomes of poor adherence to potentially effective antipsychotic therapy in patients with schizophrenia.<sup>2,6,24</sup> In the United States, fewer than 50% of Medicaid patients with schizophrenia were reported to be adherent with their prescribed antipsychotic regimen between 1998 and 2000.<sup>28</sup> Use of LAIs has resulted in increased treatment adherence, delaying symptom relapse and reducing the risk of rehospitalization in patients with schizophrenia.<sup>7,8,16,29,30</sup> This novel formulation of paliperidone palmitate with a reduced dosing frequency of 1 injection every 3 months could further mitigate the low treatment adherence in schizophrenia and improve patients' and caregivers' quality of life. The reduced dosing frequency is likely to be of particular benefit to patients with limited access to health care, eg, those who live in an underserved rural or inner city setting and have difficulties coordinating biweekly or once-monthly transportation for injection visits. When nonadherence is identified in these patients, there is a wider window than with other avail-

able antipsychotic formulations within which they can be encouraged to become adherent before plasma concentrations decrease below therapeutic thresholds.

In this study, the 3-month formulation of paliperidone palmitate significantly delayed time to relapse of schizophrenia symptoms vs placebo. Patients randomly assigned to placebo were nearly 4 times more likely to relapse during the DB phase than those who continued to receive 3-month paliperidone palmitate. Even though comparisons across studies with similar design can be confounded for multiple reasons, the estimated median time to relapse for patients switched to placebo after stabilization on various formulations of paliperidone show that 3-month paliperidone palmitate has a longer time to relapse compared with the estimates with once-monthly paliperidone palmitate and oral extended-release paliperidone (395 vs 172 and 58 days, respectively).<sup>16,26</sup> Patients at risk for sudden discontinuation from treatment could therefore benefit from 3-month paliperidone palmitate, providing protection from relapse for up to 1 year after the last dose.

The secondary end point results corroborated the primary efficacy findings. The use of a randomized withdrawal design mimics sudden discontinuation of treatment, which commonly occurs under typical clinical conditions in patients with schizophrenia. A recent survey found that among patients with schizophrenia who admit noncompliance, more than half reported stopping antipsychotic treatment without clinician knowledge or support.<sup>31</sup>

The results of this study were consistent with the efficacy and safety of once-monthly paliperidone palmitate in maintaining symptomatic control in a comparable relapse prevention study in patients with schizophrenia.<sup>16</sup> Within this study, the efficacy of 3-month paliperidone palmitate with regard to time to relapse was consistent across all subgroups assessed (age, sex, race, BMI, and geographic region). Patients enrolled in the study were first treated for 4 months with once-monthly paliperidone palmitate to establish safety and efficacy of paliperidone released from once-monthly paliperidone palmitate and to optimize the dose before the first injection of 3-month paliperidone palmitate. This study was not designed to assess the efficacy or safety of distinct doses



of 3-month paliperidone palmitate; however, it is noteworthy that a greater proportion of patients who were maintained on 525 mg eq than on 350 mg eq remained in the DB phase beyond 36 weeks.

The 3-month formulation of paliperidone palmitate has an extended apparent elimination half-life that permits dosing once every 3 months (Paulien Ravenstijn, PhD, B.R., A. Savitz, Mahesh N. Samtani, PhD, I.N., Cheng-Tao Chang, PhD, Marc De Meulder, MSc, D.W.H., and S.G., unpublished data, February 29, 2008, to May 14, 2014), offering a potential new treatment option in schizophrenia. Steady-state paliperidone plasma concentrations during the maintenance and DB phases were consistent with the observed steady-state exposure for corresponding doses of once-monthly paliperidone palmitate.<sup>10,12</sup> However, the number of plasma samples collected was limited, especially in the later part of the DB phase.

The dose of 3-month paliperidone palmitate determined by the prior dose of once-monthly paliperidone palmitate and a 3.5-fold dose conversion ratio was generally tolerable; safety findings of 3-month paliperidone palmitate observed during the 12-week maintenance phase and the subsequent DB phase of variable duration were consistent with those observed in other clinical trials with paliperidone palmitate,<sup>17,18,20,22</sup> and no new safety signals were detected. The occurrences of EPS-related TEAEs in the DB phase were generally similar to those reported in previous studies of once-monthly paliperidone palmitate.<sup>16,17,20,22</sup> Akathisia occurred more frequently with 3-month paliperidone palmitate relative to placebo in this study (4% vs 1%, respectively) than in a previous, similarly designed study (0.5% for once-monthly paliperidone palmitate vs none for placebo; D.W.H., S.G., Ujjwala Vijapurkar, PhD, Marissa Bernstein, PhD, and Anna Mendlin, PhD, unpublished data, March 4, 2005, through February 20, 2007). The mean body weight increase from OL baseline to DB end point observed for the group receiving 3-month paliperidone palmitate compared with the placebo group in this study (2.38 vs 0.55 kg, respectively) was consistent with that in the similarly designed study of once-monthly paliperidone palmitate (1.9 vs 0.0 kg, respectively).<sup>17</sup> However, the proportion of patients with an abnormal increase in body weight ( $\geq 7\%$ ) from DB baseline to end point in the group receiving 3-month paliperidone palmitate compared with the placebo group (10% vs 1%, respectively) was relatively higher than the proportion of patients in the once-monthly paliperidone palmitate group with the same body weight increase, in the similarly designed study of once-monthly paliperidone palmitate compared with placebo (6% vs 3%, respectively).<sup>17</sup> The difference in duration of follow-up during the DB phase between the 2 studies could be a possible confound in the interpretation of population mean or individual patient data for changes in body weight. Consistent with the known pharmacology of paliperidone, mean prolactin levels increased with treatment with 3-month paliperidone palmitate, more so in women than men; however, there were very few corresponding reports of potentially prolactin-related TEAEs.

While interpreting these results, certain limitations should be considered. As patients with a recent history of substance dependence were excluded from enrollment in this study, data may not be directly generalizable to this important patient sub-

Table 2. Summary of TEAEs Reported During the Double-Blind Phase in the Safety Analysis Set<sup>a</sup>

Variable	No. (%)	
	Placebo (n = 145)	3-mo Paliperidone Palmitate (n = 160)
Patients with TEAEs	84 (58)	99 (62)
Possibly drug-related TEAE	27 (19)	54 (34)
TEAE leading to drug withdrawal	1 (1)	0
Patients with $\geq 1$ serious TEAE	15 (10)	4 (3)
TEAEs reported in $\geq 2\%$ of patients in either group		
Headache	6 (4)	14 (9)
Anxiety	16 (11)	13 (8)
Insomnia	17 (12)	11 (7)
Nasopharyngitis	2 (1)	9 (6)
Upper respiratory tract infection	3 (2)	6 (4)
Cough	3 (2)	5 (3)
Urinary tract infection	2 (1)	5 (3)
Influenza	3 (2)	3 (2)
Schizophrenia	15 (10)	2 (1)
Weight decreased	11 (8)	2 (1)
Agitation	3 (2)	2 (1)
Decreased appetite	3 (2)	1 (1)
Irritability	3 (2)	1 (1)
Suicidal ideation	3 (2)	0
EPS-related TEAEs	5 (3)	13 (8)
Akathisia	1 (1)	7 (4)
Diabetes mellitus- and hyperglycemia-related TEAEs	8 (6)	4 (3)
Blood glucose level increased	3 (2)	3 (2)
Hyperglycemia	4 (3)	0
Weight gain-related TEAEs	5 (3)	15 (9)
Weight increased	5 (3)	14 (9)
Injection site-related TEAEs	0	6 (4)
Prolactin-related TEAEs	0	1 (1)
Amenorrhea	0	1 (2) <sup>b</sup>

Abbreviations: EPS, extrapyramidal symptom; TEAEs, treatment-emergent adverse events.

<sup>a</sup> The TEAEs reported herein occurred during the double-blind phase; if a patient developed a TEAE during the open-label phase (either transition or maintenance) and the TEAE did not worsen during the double-blind phase, it would not be captured.

<sup>b</sup> Sample size was 42 women.

group that is particularly vulnerable to relapse with alternate, shorter-acting formulations of atypical antipsychotics. The relapse prevention design was based on the principle of enrichment; clinical stability was required before entry into maintenance and DB phases. Hence, results of the DB analysis set may not reflect the true efficacy of 3-month paliperidone palmitate for relapse prevention in all patients with schizophrenia irrespective of their initial response to once-monthly paliperidone palmitate as monotherapy in the treatment of acute worsening of symptoms. The safety profiles of the 1-month and 3-month formulations of paliperidone palmitate within this study cannot be directly compared as the



formulations were administered sequentially, ie, during distinct phases of the study, and once-monthly paliperidone palmitate was provided as OL treatment only. In addition, the fixed-dosing regimen implemented during the DB phase of this study prevents evaluation of the ratio of benefit to risk for distinct dose levels of 3-month paliperidone palmitate for relapse prevention. In clinical practice, dose selection of 3-month paliperidone palmitate will be informed by the dose of once-monthly paliperidone palmitate, affording an optimal ratio of benefit to risk as determined for individual patients in the period of prior treatment with once-monthly paliperidone palmitate. Because of differences in duration of follow-up and exposure in the DB phase, comparison of data for secondary efficacy and safety end points between treatment groups, as based on changes in continuous or categorical variable over time (eg, body weight, BMI), should be interpreted with caution within this study and with reference to the similarly designed study of once-monthly paliperidone palmitate. Data will be available to compare the safety profiles of the 1-month and 3-month formulations of paliperidone palmitate directly when an ongoing noninferiority study of the 2 LAI formulations of

paliperidone for the treatment of patients with schizophrenia is completed (clinicaltrials.gov identifier NCT01515423).

## Conclusions

Compared with placebo, the 3-month formulation of paliperidone palmitate significantly delayed time to first relapse in patients with schizophrenia previously treated with once-monthly paliperidone palmitate for at least 4 months. Furthermore, 3-month paliperidone palmitate was generally tolerable with a safety profile consistent with other marketed formulations of paliperidone. The 3-month formulation allows patients to maintain therapeutic paliperidone plasma levels with fewer injections, which could subsequently improve functional outcome and quality of life with a sufficient follow-up period. The extended dosing interval may offer particular advantages for patients and their caregivers or families who are struggling with continuous treatment or have limited health care access and are thus at increased relapse risk from treatment discontinuation.

## ARTICLE INFORMATION

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**Study concept and design:** Berwaerts, Liu, Gopal, Nuamah, Xu, Savitz, Coppola, Remmerie, Hough. **Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Berwaerts, Liu, Gopal, Nuamah, Xu, Hough.

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**Statistical analysis:** Liu, Gopal, Nuamah, Xu.

**Obtained funding:** Gopal.

**Administrative, technical, or material support:** Berwaerts, Liu, Gopal, Savitz, Coppola, Schotte, Hough.

**Study supervision:** Gopal, Coppola, Hough.

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**Additional Contributions:** Shalini Nair, PhD, SIRO Clinpharm Pvt Ltd, Maharashtra, India, provided writing assistance and Wendy P. Battisti, PhD, Janssen Research & Development, LLC, Titusville, New Jersey, provided additional editorial and writing support for the manuscript; they received compensation from the funding sponsor for these contributions. Navid Samad, MD, Samad Pharma and Biotech Consulting, LLC, White Plains, New York, contributed to data analysis; he received compensation as a paid consultant. Dean Najarian, PharmD, Janssen Pharmaceuticals, Titusville, contributed to medical monitoring; he received compensation as an employee of the sponsor. Christoph Correll, MD, Zucker Hillside Hospital, Glen Oaks, New York, L. Frederick Jarskog, MD, North Carolina Psychiatric Research Center, Raleigh, Mary F. Johnson, PhD, MJBioStat, Spring Lake, New Jersey, Joseph Peuskens, MD, PhD, Catholic University of Louvain, Kortenberg, Belgium, and Rene S. Kahn, MD, PhD, University Medical Center Utrecht, Utrecht, the Netherlands, were members of the independent data monitoring committee; they received a stipend from the contract research organization that administered the interim analysis. We thank the study participants, without whom this study would never have been accomplished, and the investigators for their participation in this study.

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**4.3. Overview of Study Drug Administration**

An overview of the dosing administration schedule in the transition, maintenance and double-blind phases of the study is provided in Table 3.

<b>Table 3. Dosing Administration Schedule</b>												
	Transition Phase					Maintenance Phase			Double-blind Phase			
Visit	2	3	4	5	6	8	9	10	11	12	13	Every 12 weeks
Day	1*	8*	36	64	92	120	148	176	204	232	260	
PP1M	150	100	50-150	50-150	50-150	--	--	--	--	--	--	--
Dose	mg eq.	mg eq.	mg eq.	mg eq.	mg eq.							
Muscle	D	D	D or G	D or G	D or G	D or G			D or G			D or G
Flexible or Fixed	Fixed	Fixed	Flexible	Flexible	Fixed†	Fixed‡	--	--	Fixed‡	--	--	Fixed‡
PP3M/ Placebo Dose	--	--	--	--	--	X	--	--	X	--	--	X

\*Refer to Table 1& 2 respectively, for patients who are stable on PP1M at study entry and for patients who are switching from other depot antipsychotics

†Dose on this visit should be the same as given on Visit 5 (Day 64)

‡The dose of PP3M given will be a 3.5-fold multiple of the PP1M dose given on Visit 6 (Day 92)

D denotes deltoid muscle. G denotes gluteal muscle. PP1M denotes=paliperidone palmitate 1 month formulation. PP3M denotes paliperidone palmitate 3 month formulation.

**4.3.1. Dose during Transition Phase**

During the transition phase, all patients will receive PP1M injections. All patients who are not switching from other depot antipsychotics will receive the first injection of 150 mg eq. on Day 1 and the second injection of 100 mg eq. on Day 8, both in the deltoid muscle. Patients may be flexibly dosed on Days 36 and 64 with doses of 50, 75, 100, or 150 mg eq. At Day 92, patients are to receive the dose of PP1M that was administered at Day 64. The choice of the dose to be administered at Days 36 and 64 will be based on the severity of the patient's symptoms, safety and tolerability issues, and previous dose levels of antipsychotic medication needed to keep symptoms under control. After injection of PP1M on Days 1 and 8, subsequent doses can be administered in either the deltoid or gluteal muscle.

**4.3.2. Dose during Maintenance Phase**

During the 12-week maintenance phase, patients will receive a dose of PP3M that is a 3.5-fold multiple of the final PP1M dose administered on Day 92. During this phase, a single dose of PP3M will be administered on Day 120. The dosing conversion between PP1M and PP3M doses should be based upon that provided in Table 4.

26

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**Table 4. Conversion Between PP1M Dose and PP3M Doses Using 3.5-Fold Multiple**

PP1M Dose (mg paliperidone palmitate)	PP1M Dose (mg eq. paliperidone)	PP3M Dose (mg paliperidone palmitate)	PP3M Dose (mg eq. paliperidone)
78 mg	50 mg eq.	273 mg	175 mg eq.
117 mg	75 mg eq.	410 mg	263 mg eq.
156 mg	100 mg eq.	546 mg	350 mg eq.
234 mg	150 mg eq.	819 mg	525 mg eq.

PP1M denotes paliperidone palmitate 1 month formulation. PP3M denotes paliperidone palmitate 3 month formulation.

**4.3.3. Dose during Double-blind Relapse Prevention Phase**

During the double-blind phase, patients will receive fixed dose injections of either PP3M or placebo (20% Intralipid solution) every 3 months. The dose range for PP3M will be 175, 263, 350, or 525 mg eq. Patients assigned to PP3M in the double-blind phase will receive the same dose of study drug that was administered on Day 120 of the maintenance phase. Dosing during the double-blind phase will be fixed. Changing of the dose during the double-blind phase will not be allowed. Supplementation with oral antipsychotics will also not be allowed. The selected muscle for injection will alternate between the left and the right sides. The injection site may be changed (between deltoid and gluteal muscles) at the investigator's discretion if needed to mitigate local tolerability concerns.

**Injection Guidelines**

It is critical to shake the syringe vigorously for 15 seconds before administration.

**Needle Size**

For deltoid injections, it is required that a 1.5 inch needle be used for patients  $\geq 200$  lb (90 kg). For patients  $< 200$  lb (90 kg), a 1 inch needle is to be used.

For gluteal injections all injections should be administered with a 1.5 inch needle (regardless of a patient's weight).

**eTable 2. Conversion Between PP1M and PP3M Doses**

PP1M Dose	PP3M Dose (3.5-Fold Multiple)	PP1M Dose	PP3M Dose (3.5-Fold Multiple)
(mg paliperidone palmitate)		(mg eq. paliperidone)	
78 mg	273 mg	50 mg eq.	175 mg eq.
117 mg	410 mg	75 mg eq.	263 mg eq.
156 mg	546 mg	100 mg eq.	350 mg eq.
234 mg	819 mg	150 mg eq.	525 mg eq.

Abbreviations: PP3M, paliperidone palmitate 3-month formulation; PP1M, paliperidone palmitate 1 month formulation.

**eTable 3. Frequency Distribution of Relapse Types and Reasons During Double-Blind Phase—Interim and Final Analyses (Intent-to-Treat [DB] Analysis Set)**

	No. (%)					
	Interim Analysis			Final Analysis		
	Placebo (N=135)	PP3M (N=148)	Total (N=283)	Placebo (N=145)	PP3M (N=160)	Total (N=305)
Total patients with relapse	31 (23)	11 (7)	42 (15)	42 (29)	14 (9)	56 (18)
Psychiatric hospitalization	6 (4)	2 (1)	8 (3)	10 (7)	2 (1)	12 (4)
PANSS total score	26 (19)	8 (5)	34 (12)	35 (24)	10 (6)	45 (15)
Increase of $\geq 25\%$ in total PANSS score	25 (19)	8 (5)	33 (12)	34 (23)	10 (6)	44 (14)
10-point increase in total PANSS score	1(1)	0	1(<1)	1(1)	0	1(<1)
Deliberate self-injury, violent behavior	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (<1)
Suicidal or homicidal ideation	1 (1)	2 (1)	3 (1)	2 (1)	3 (2)	5 (2)
PANSS items (P1, P2, P3, P6, P7, G8)	5 (4)	1 (1)	6 (2)	7 (5)	1 (1)	8 (3)

Abbreviations: PANSS, Positive and Negative Syndrome scale; PP3M, paliperidone palmitate 3-month formulation. For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P6 (suspiciousness/persecution), P7 (hostility), and G8 (uncooperativeness).



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(54) **DOSING REGIMEN ASSOCIATED WITH  
LONG ACTING INJECTABLE  
PALIPERIDONE ESTERS**

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(57) **ABSTRACT**

The present invention provides a method of treating patients  
in need of treatment with long acting injectable paliperidone  
palmitate formulations.

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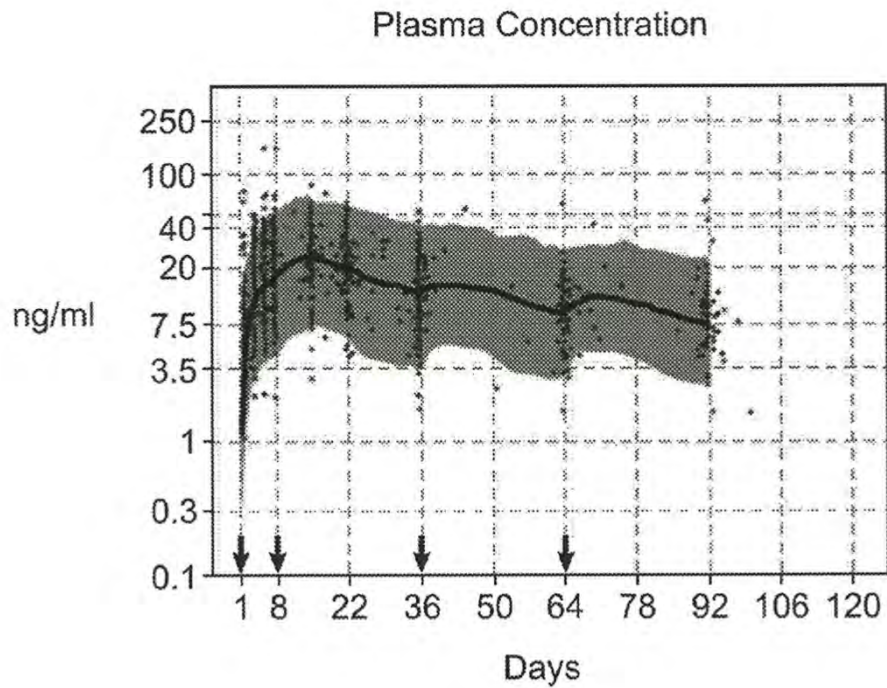
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**Appx10465**



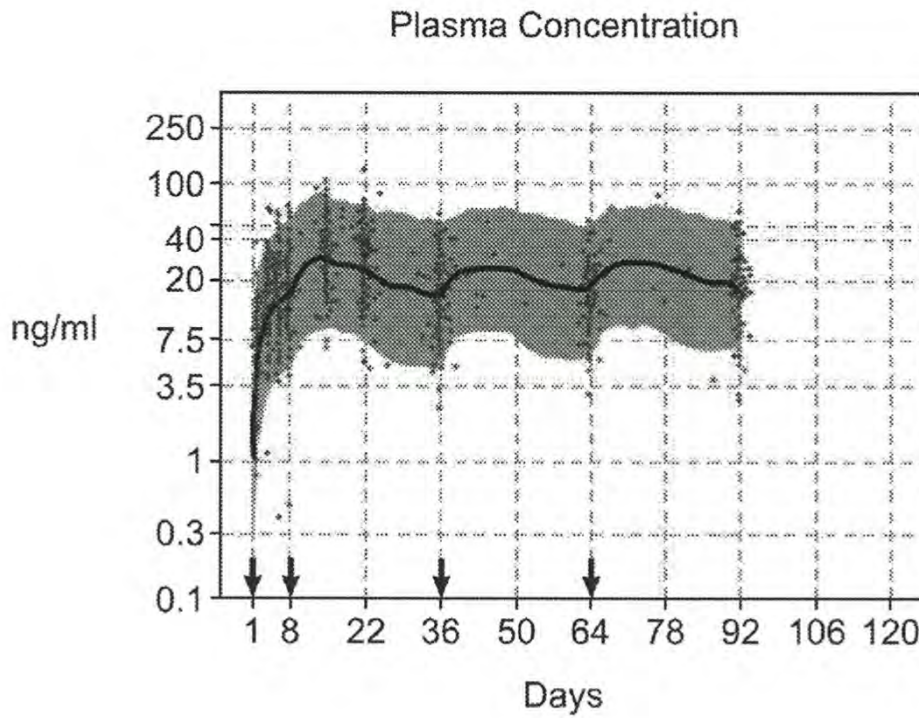
**FIG. 1**



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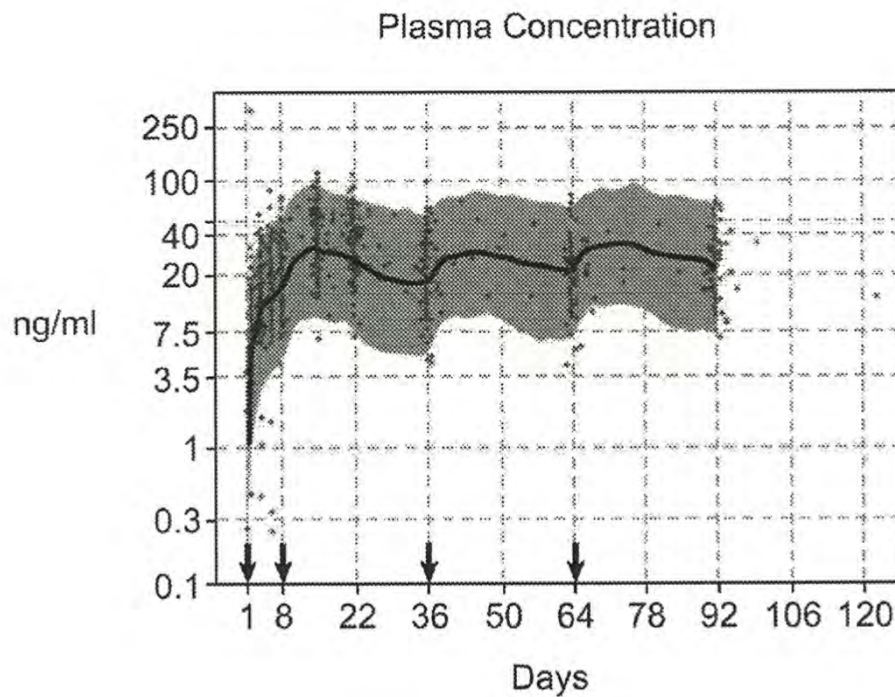
**FIG. 2**



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**FIG. 3**



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US 2009/0163519 A1

Jun. 25, 2009

1

## DOSING REGIMEN ASSOCIATED WITH LONG ACTING INJECTABLE PALIPERIDONE ESTERS

### FIELD OF THE INVENTION

[0001] This invention relates to a method of treating patients in need of treatment with long acting injectable paliperidone palmitate formulations.

### BACKGROUND OF THE INVENTION

[0002] Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Conventional antipsychotics were introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

[0003] Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine  $D_2$  and serotonin (5-hydroxytryptamine type 2A) antagonism of the second-generation, atypical antipsychotic drugs. Paliperidone is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

[0004] Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other diseases that are normally treated with antipsychotic medications. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

[0005] Many patients with these mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. compliance problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies.

[0006] Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly, which may greatly enhance compliance with dosing. Paliperidone palmitate was formulated as an aqueous nano suspension as is described in U.S. Pat. Nos. 6,577,545 and 6,555,544. However, after the data was analyzed from the clinical trials of this formulation it was discovered that the absorption of paliperidone from these injections was far more complex than was originally anticipated. Additionally, attaining a potential therapeutic plasma level of paliperidone in patients was discovered to be dependent on the site of injection until steady state concentration is reached. Due to the challenging nature of ensuring an optimum plasma concentration-time profile for treating

patients with paliperidone it is desirable to develop a dosing regimen that fulfills this goal in patients in need of treatment.

### SUMMARY OF THE INVENTION

[0007] In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation on between about the 34<sup>th</sup> and about the 38th day of treatment.

[0008] In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose from about 100 mg to about 150 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 150 mg-eq. of paliperidone as a paliperidone ester in a sustained release formulation approximately monthly from the date of the second loading dose.

[0009] In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose from about 100 mg-eq. to about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on between about the 34th day and the 38th day of treatment.

[0010] In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a

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US 2009/0163519 A1

Jun. 25, 2009

2

maintenance dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

[0011] In another embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose from about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

[0012] In yet another embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a renally impaired psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 mg-eq. to about 75 mg-eq of paliperidone as a paliperidone palmitate in a sustained release formulation on between about the 34<sup>th</sup> and about the 38th day of treatment.

[0013] In yet another embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a renally impaired psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 100 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly a second loading dose of about 75 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 mg-eq. to about 75 mg-eq of paliperidone as a paliperidone palmitate in a sustained release formulation approximately monthly from the date of the second loading dose.

[0014] In a further embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 75 mg-eq of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance

dose of from about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th day and the 38th day of treatment.

[0015] In one embodiment of the present invention there is provided a dosing regimen for administering paliperidone esters to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid a first loading dose of about 150 mg-eq. of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; thereafter administering intramuscularly a second maintenance dose of from about 25 mg-eq. to about 100 mg-eq of paliperidone as a paliperidone palmitate formulated in a sustained release formulation between about the 6th to 10th day of treatment; and administering intramuscularly in the gluteal a maintenance dose of about 25 to about 100 mg-eq. of paliperidone as a paliperidone palmitate in a sustained release formulation on between about the 34<sup>th</sup> and about the 38th day of treatment.

[0016] In a further embodiment of the present invention there is provided a dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose from about 150 mg-eq. of paliperidone as a paliperidone palmitate ester in a sustained release formulation on the first day of treatment; thereafter administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th day and the 38th day of treatment.

[0017] This and other objects and advantages of the present invention may be appreciated from a review of the present applications.

#### BRIEF DESCRIPTION OF THE FIGURES

[0018] FIG. 1 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 25 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

[0019] FIG. 2 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 100 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

[0020] FIG. 3 shows the observed versus the population pharmacokinetics model simulation for plasma paliperidone concentrations for paliperidone palmitate 150 mg eq. in the deltoid on day 1, followed by 150 mg eq. in either the deltoid or gluteus on days 8, 36, and 64.

#### DETAILED DESCRIPTION

[0021] We have discovered after extensive analysis of the clinical data that paliperidone palmitate due to its dissolution rate-limited absorption exhibits flip-flop kinetics, where the apparent half-life is controlled by the absorption rate constant. Additionally the volume of injected drug product also

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US 2009/0163519 A1

Jun. 25, 2009

3

impacts the apparent rate constant. It was also discovered that deltoid injections result in a faster rise in initial plasma concentration, facilitating a rapid attainment of potential therapeutic concentrations. Consequently, to facilitate patients' attaining a rapid therapeutic concentration of paliperidone it is preferred to provide the initial loading dose of paliperidone palmitate in the deltoids. The loading dose should be from about 100 mg-eq. to about 150 mg-eq. of paliperidone provided in the form of paliperidone palmitate. After the first or more preferably after the second loading dose injection patients will be approaching a steady state concentration of paliperidone in their plasma and may be injected in either the deltoid or the gluteal muscle thereafter. However, it is preferred that the patients receive further injections in the gluteal muscle.

[0022] In view of these discoveries the recommended dosing regimen for patients to attain a therapeutic plasma level of paliperidone is for patients to receive the first dose of paliperidone palmitate on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment or monthly  $\pm 7$  days after the second dose. More preferably the patients will be administered a first dose on day 1, a second dose on day 8 and a third dose on or about day 36 of treatment or approximately monthly  $\pm 3$  days after the second dose. The first two doses will preferably be injected in the deltoid muscle. Thereafter paliperidone palmitate will be administered by injection approximately once a month (e.g. monthly  $\pm 7$  days or approximately once every four weeks) thereafter. To assure that a potential therapeutic plasma level of paliperidone is attained at least a first loading dose of 150 mg-eq of paliperidone as a paliperidone palmitate ester should be administered on day one of treatment. Preferably the first two doses will be loading dose of between from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate ester to assure that a potential therapeutic plasma level of paliperidone is attained by the patient. The subsequent doses thereafter will drop to a therapeutic maintenance dose of from about 25 mg-eq. to 150 mg-eq. per month ( $\pm 7$  days). Preferably the maintenance dose will be from about 25 mg eq. to about 100 mg eq; more preferably the maintenance dose will be from about 25 mg eq. to about 75 mg eq; and most preferably the maintenance dose initially will be about 50 mg eq., or more preferably the maintenance dose initially will be about 75 mg eq. which may be administered intramuscularly into the deltoid or gluteal muscle, but more preferably will be administered in the gluteal muscle. Those of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patients condition (response to the medication and renal function).

[0023] Since paliperidone is mainly eliminated through the kidneys, patients with renal impairment will have a higher total exposure to paliperidone after i.m. injections of paliperidone palmitate. For patients with renal impairment it would be desirable to adjust the loading doses to account for the increased exposure levels of patients with renal impairment. For patients with mild renal impairment the loading doses should be reduced to 75 mg-eq. for the first two loading doses. The maintenance doses should range from about 25 mg-eq. to about 75 mg-eq. and more preferably with range from about 25 mg-eq. to about 50 mg-eq. The doses would be administered on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment. More preferably the patients will

be administered a first dose on day 1, a second dose on day 8 and a third dose on day 36 of treatment. The first two doses will preferably be injected in the deltoid muscle. Thereafter paliperidone palmitate will be administered by injection approximately once a month (e.g. one a month  $\pm 7$  days or once every four weeks) thereafter. For the purpose of this patent application renal function is estimated by glomerular filtration rate (GFR) usually measured by the creatinine clearance (best calculated from a 24-hour urine collection). Creatinine clearance may be estimated by the Cockcroft and Gault method based on serum creatinine concentration, as described in Prediction of creatinine clearance from serum creatinine. Nephron 1976; vol 16. pages 31-41. Patients with mild renal impairment have a creatinine clearance of 50 to  $<80$  mL/minute.

[0024] It is recommended that the second initiation dose of paliperidone palmitate be given about one week (6-10 days) after the first dose. To avoid a missed dose, patients may be given the second dose 2 days before or after the one-week time point. Similarly, the third and subsequent injections after the initiation regimen are recommended to be given monthly. To avoid a missed monthly dose, patients may be given the injection up to 7 days before or after the monthly time point.

[0025] After initiation, the recommended injection cycle of paliperidone palmitate is monthly. If less than 6 weeks have elapsed since the last injection, then the previously stabilized dose should be administered as soon as possible, followed by injections at monthly intervals.

[0026] If more than 6 weeks have elapsed since the last injection, reinitiation with the same dose the patient was previously stabilized to should be resumed in the following manner: 1) a deltoid injection as soon as practically possible, followed by 2) another deltoid injection one week later, and 3) resumption of either deltoid or gluteal dosing at monthly intervals.

[0027] If more than 6 months have elapsed since the last injection, it is recommended to re-initiate dosing as described above.

[0028] Additionally, in this patient population needle length and BMI index are two related variables that need to be considered to assure patients attain therapeutic concentration of paliperidone in the desired time frame. Patients with high BMI had lower plasma concentration of paliperidone and a lessened treatment response. The lower initial plasma concentration in high BMI patients was likely due to unintended partial or complete injection into adipose tissue, instead of deep injection into muscle. However, once steady-state plasma concentration are attained BMI no longer influenced plasma concentrations or clinical efficacy. From these observations it was determined that for patients weighing  $<90$  kg ( $<200$  lb) a 1-inch needle will be of adequate length to use in injections to reach the muscle tissue for deltoid injections with preferably a 23 gauge needle. However, for patients with high BMIs,  $\geq 90$  kg ( $\geq 200$  lb) a 1.5-inch needle should be used for deltoid injections. For gluteal muscle injections a 1.5-inch needle should be used. Preferably the 1.5-inch needle will be a 22-gauge needle.

[0029] Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, which contains a racemic mixture of (+)- and (-)-paliperidone, which are described in U.S. Pat. No. 5,254,556 (incorporated herein by reference). The chemical name for paliperidone palmitate is (+)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-

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PTX-115

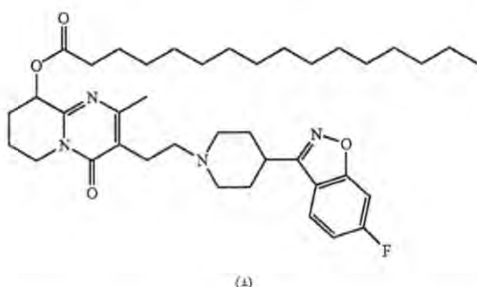
PTX-0115\_0007

US 2009/0163519 A1

Jun. 25, 2009

4

piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate. The structural formula is:



[0030] Paliperidone esters may be formulated with pharmaceutical excipients into injectable dosage forms as described in U.S. Pat. No. 5,254,556 and U.S. Pat. No. 6,077,843 (incorporated herein by reference). Injectable formulations may be formulated in aqueous carriers.

[0031] Currently it is preferred to administer paliperidone palmitate in a once monthly aqueous depot. Suitable aqueous depot formulations are described in U.S. Pat. No. 6,077,843 (incorporated herein by reference). The aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would be of an average size of less than 2000 nm to about 100 nm. Preferably the nano particles would have an average particle size (d50) of from about 1600 nm to 400 nm and most preferably about 1400 nm to 900 nm. Preferably the d90 will be less than about 5000 nm and more preferably less than about 4400 nm. As used herein, an effective average particle size (d50) of less than 2,000 nm means that at least 50% of the particles have a diameter of less than 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least 90%, e.g., 5,000 nm. Most preferably, 90% of the particles have a size of less than 4,400 nm.

[0032] Suitable aqueous nano particle depot formulations are described in U.S. Pat. No. 6,555,544 (incorporated herein by reference). In one embodiment of the present invention the formulation would comprise nanoparticles, a surfactant, a suspending agent, and optionally one or more additional ingredients selected from the group consisting of preservatives, buffers and an isotonicizing agents. Useful surface modifiers are believed to include those that physically adhere to the surface of the active agent but do not chemically bond thereto.

[0033] Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethyl-

ene sorbitan fatty acid esters, e.g., the commercially available TWEENS™, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminate silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

[0034] Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as PLURONIC™ F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as TETRONIC™ 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT™ (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; DUPONOL P which is a sodium lauryl sulfate available from DuPont; TRITON X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; TWEEN™, 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Specialty Chemicals; SPAN™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids; ARLACEL™ 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; CARBOWAX™ 3550 and 934 which are polyethylene glycols available from Union Carbide; CRODESTA™ F110 which is a mixture of sucrose stearate and sucrose distearate available from Croda Inc.; CRODESTA™ SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is C<sub>18</sub>H<sub>17</sub>CH<sub>2</sub> (CON(CH<sub>3</sub>)CH<sub>2</sub>(CHOH)<sub>4</sub>CH<sub>2</sub>O)<sub>2</sub>. The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic™ F108 and Pluronic™ F68.

[0035] Pluronic™ F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula HO(CH<sub>2</sub>CH<sub>2</sub>O)<sub>x</sub>[CH(CH<sub>3</sub>)CH<sub>2</sub>O]<sub>y</sub>[CH<sub>2</sub>CH<sub>2</sub>O]<sub>z</sub>H in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag NONIONIC™ 1108-F available from Hodag, and SYNPERONIC™ PE/F108 available from ICI Americas.

[0036] The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the antipsychotic agent, etc. The specific surface modifier preferably is present in an amount of 0.1 to 1 mg per square meter surface area of the paliperidone palmitate. It is preferred in the case of paliperidone palmitate (9-hydroxyrisperidone palmitate) to use PLURONIC™ F 108 as a surface modifier, a relative amount (w/w) of both ingredients of approximately 6:1 is preferred.

EXPERTS\_MYL\_002400  
PTX-115

PTX-0115\_0008



US 2009/0163519 A1

Jun. 25, 2009

5

[0037] The particles of this invention can be prepared by a method comprising the steps of dispersing paliperidone palmitate in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the antipsychotic agent to an effective average particle size of less than 2,000 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

[0038] A general procedure for preparing the particles of this invention includes (a) obtaining paliperidone palmitate in micronized form; (b) adding the micronized paliperidone palmitate to a liquid medium to form a premix; and (c) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the effective average particle size.

[0039] The paliperidone palmitate in micronized form may be prepared using techniques known in the art. It is preferred that the particle size of the micronized paliperidone palmitate be less than about 100  $\mu\text{m}$  as determined by sieve analysis. If the particle size of the micronized paliperidone palmitate is greater than about 100  $\mu\text{m}$ , then it is preferred that the particles of paliperidone palmitate be reduced in size to less than 100  $\mu\text{m}$ .

[0040] The micronized paliperidone palmitate can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of paliperidone palmitate in the liquid medium (weight by weight percentage) can vary widely and depends on the selected antipsychotic agent, the selected surface modifier and other factors. Suitable concentrations of paliperidone palmitate in compositions vary between 0.1 to 60%, preferably is from 0.5 to 30%, and more preferably, is approximately 7% (w/v). It is currently preferred to use a concentration of about 100 mg eq of paliperidone per ml or about 156 mg of paliperidone palmitate per ml.

[0041] A more preferred procedure involves the addition of a surface modifier to the premix prior to its subjection to mechanical means to reduce the effective average particle size. The concentration of the surface modifier (weight by weight percentage) can vary from 0.1% to 90%, preferably from 0.5% to 80%, and more preferably is approximately 7% (w/v).

[0042] The premix can be used directly by subjecting it to mechanical means to reduce the effective average particle size in the dispersion to less than 2,000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the antipsychotic agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation such as, for example, a roller mill or a Cowles type mixer, until a homogeneous dispersion is achieved.

[0043] The mechanical means applied to reduce the effective average particle size of the antipsychotic conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills—such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is anywhere between 0.1 and 1 Pa·s. For ball milling, the apparent viscosity of the premix preferably is anywhere between 1 and 100 mPa·s.

[0044] The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than 3 mm and,

more preferably, less than 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles having levels of contamination which are acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and 95% ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than 2.5 g/cm<sup>3</sup> and include 95% ZrO stabilized with magnesia and polymeric beads.

[0045] The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For rolling mills, processing times of up to two days or longer may be required.

[0046] The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than 30° C. to 40° C. are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

[0047] The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed by, for example, shaking vigorously. Optionally, the dispersion can be subjected to a sonication step using, for example, a ultrasonic power supply.

[0048] Aqueous compositions according to the present invention conveniently further comprise a suspending agent and a buffer, and optionally one or more of a preservative and an isotonicizing agent. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonicizing agent.

[0049] Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylenic- and polyoxy-propylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of 0.5 to 2%, most preferably 1% (w/v). Suitable wetting agents for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a concentration of 0.5 to 3%, more preferably 0.5 to 2%, most preferably 1.1% (w/v).

[0050] Suitable buffering agents are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 7.5. Particularly preferred is the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9% (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6% (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein.

[0051] Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic

EXPERTS\_MYL\_002401  
PTX-115

PTX-0115\_0009



US 2009/0163519 A1

Jun. 25, 2009

6

acid, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-gamma-piccolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to 2% (w/v), preferably up to 1.5% (w/v).

[0052] Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from 0 to 10% (w/v) isotonizing agent. Mannitol may be used in a concentration from 0 to 7% More preferably, however, from about 1 to about 3% (w/v), especially from about 1.5 to about 2% (w/v) of one or more electrolytes are used to render the suspension isotonic, apparently because ions help to prevent flocculation of the suspended ester. In particular, electrolytes of the buffer serve as isotonizing agent.

[0053] A particularly desirable feature for an injectable depot formulation relates to the ease with which it can be administered. In particular such an injection should be feasible using a needle as fine as possible in a span of time which is as short as possible. This can be accomplished with the aqueous suspensions of the present invention by keeping the viscosity below about 75 mPa·s, preferably below 60 mPa·s. Aqueous suspensions of such viscosity or lower can both easily be taken up in a syringe (e.g. from a vial), and injected through a fine needle (e.g. a 21 G 1½ inch, 22 G 2 inch, 22 G 1¼ inch or 23 G 1 inch needle). The preferred needles for injection are 22 G 22 G 1½ inch regular wall and 23 G 1½ inch regular wall needles.

[0054] Ideally, aqueous suspensions according to the present invention will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular, such a composition will comprise by weight based on the total volume of the composition: (a) from 3 to 20% (w/v) of the prodrug; (b) from 0.5 to 2% (w/v) of a wetting agent; (c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5); (d) from 0.5 to 2% (w/v) of a suspending agent; (e) up to 2% (w/v) preservatives; and (f) water q.s. ad 100%. Preferably the aqueous suspension will be made under sterile conditions and no preservatives will be used. Appropriate methods to aseptically prepare paliperidone palmitate are described in WO 2006/114384 which is hereby incorporated by reference herein.

[0055] The preferred aqueous dosage form contains inactive ingredients that are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection. The mg of compound delivered in such a dosage form to the patient may be from 25 to about 150 mg (e.g. 25 mg, 50 mg, 75 mg, 100 mg, 150 mg) injectable dosage form.

[0056] The term "psychiatric patient" as used herein, refers to a human, who has been the object of treatment, or experiment for a "mental disorder" and "mental illness" refer to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone esters (e.g. paliperidone palmitate), can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evi-

denced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform disorders, in DSM-IV-TR such as category 295.xx. Bipolar Disorder refers to a condition characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be associated with psychotic features include, but are not limited to the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The numbers in parenthesis refer to the DSM-IV-TR categories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress. Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusions (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delu-

EXPERTS\_MYL\_002402  
PTX-115

PTX-0115\_0010

US 2009/0163519 A1

Jun. 25, 2009

7

sions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

der, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

[0057] The following non-limiting examples are provided to further illustrate the present invention.

[0058] The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

[0059] Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. In general it is contemplated that an effective amount of paliperidone for the treatment of mental disorders would be from about 0.01 mg/kg to about 2 mg/kg body weight. For the present invention it is preferred to dose patients with 25 mg-eq. to about 150 mg eq. paliperidone. The amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g. 156 mg corresponds to paliperidone 100 mg). In one embodiment of present invention wherein paliperidone palmitate is administered by intramuscular injection once per month is preferred.

#### Example 1

##### Paliperidone Palmitate Formulations

##### a) Crystallization in Stainless Steel Reactor of 50 L

[0060] All equipment was sterilized using dry heat sterilization.

[0061] A stainless steel reactor was charged with 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one palmitate ester and ethanol parenteral grade (8 L/kg) and heated to reflux temperature (78-79° C.) while stirring. The product dissolved at about 70° C. The solution was filtered at 76° C. over a sterile 0.22 µm filter into a sterile crystallization reactor. The sterile filter was then washed with heated ethanol (1 L/kg).

[0062] The filtrate was reheated to reflux and then cooled to room temperature whereupon the product crystallized. The thus obtained suspension was reheated again. The solution was cooled using differing cooling gradients (in consecutive experiments, the mixture was reheated and cooled again; after each cooling gradient, a sample was taken and isolated using a filter. The crystals were dried in vacuo at 50° C. in Tyvek bags so as to prevent dust formation and the particle characteristics were determined.

[0063] Different batches were run, yielding product with a particle size distribution measured by laser diffraction as shown in Table 1.

EXPERTS\_MYL\_002403  
PTX-115

PTX-0115\_0011

US 2009/0163519 A1

Jun. 25, 2009

8

TABLE 1

Cooling  rate	Crystallization						Particle size distribution		
	Calculated cooling  gradient	Tmax	start at . . .		start cooling				
			(° C.)		(° C.)				
			(° C./min)	Treactor	Treactor	Tjacket	Treactor	(µm)	(µm)
1° C./min	0.95	78	63.5	60.2	77.5	156	65	16	
ASAP	3.2	75.7	61.2	17.5	75	119	36	9.2	
0.5° C./min	0.48	75.7	63.8	62.7	75	192	80	20	
0.5° C./min	0.48	75.7	63.8	62.7	75	189	81	23	
0.7° C./min	0.81	75.7	61.7	58.9	75	113	41	11	
1° C./min	0.92	75.7	62.1	54.9	75	128	52	13	

## b) Formulation of Composition

[0064] Table 2 provides the formulation for the F013 formulation. The F011 formulation contained the same ingredients, with the exception of citric acid and NaOH, which were not present in the F011 formulation. Since the F011 formulation does not contain NaOH or citric acid, they are not part of the aqueous phase that is added to the milled concentrate of the F011 formulation. Therefore, the concentration of buffer salts in the aqueous phase of the F011 formulation is slightly different to make the formulation isotonic.

TABLE 2

Name	Amount Required	
	Per ml	Quantity for 24 L
Paliperidone palmitate (sterile grade)	156 mg	3.744 kg
Polysorbate 20 parenteral	12 mg	288 g
Citric acid monohydrate parenteral	5 mg	120 g
Disodium hydrogen phosphate anhydrous parenteral	5 mg	120 g
Sodium dihydrogen phosphate monohydrate parenteral	2.5 mg	60 g
Sodium Hydroxide all use	2.84 mg	68 g
Polyethylene Glycol 4000 parenteral	30 mg	720 g
Water for injections q.s. ad	1000 µl	24 L

## Equipment

- [0065] stainless steel (SS) containers
- [0066] Grinding media (Zirconium beads)+stainless steel (SS) grinding chamber
- [0067] 0.2 µm filters
- [0068] 40 µm filter
- [0069] Filling unit
- [0070] Autoclave
- [0071] Dry heat oven

## Manufacturing

[0072] Zirconium beads were cleaned and rinsed using water for injections and then depyrogenised by dry heat (120 min at 260° C.). Water for injections was transferred into a SS container. Polysorbate 20 was added and dissolved by mixing. The solution was sterilized by filtration through a sterile 0.2 µm filter into a sterilized SS container. Paliperidone palmitate ester (sterile grade) as prepared in the previous examples was dispersed into the solution and mixed until

homogeneous. The suspension was milled aseptically in the grinding chamber using Zirconium beads as grinding media until the required particle size was reached. The suspension was filtered aseptically through a 40 µm filter into a sterilized SS container

[0073] Water for injections was transferred into a SS container, citric acid monohydrate parenteral, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide all use, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through a sterile 0.2 µm filter and transferred aseptically into the suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes. The target dose volume was between 0.25 ml and 1.50 ml depending on the dose needed.

TABLE 3

Dose volume	Target limit	lower limit	upper limit
0.25 ml-1.00 ml	identical to dose volume	target limit - (target limit × 0.05)	target limit × 1.05
1.25 ml-1.50 ml	identical to dose volume	target limit - (target limit × 0.025)	target limit × 1.025

## Sterilization

[0074] All aseptic manipulations and sterilization processes were carried out according to FDA and European regulatory guidelines.

## Apparatus

- [0075] Sterilization was done by steam sterilization ( $F_0 \geq 15$ ) of following equipment:
- [0076] SS containers
- [0077] Zirconium beads+grinding chamber
- [0078] 0.2 µm filters
- [0079] 40 µm filter
- [0080] filling pump
- [0081] Immediate Container
- [0082] 1 ml long transparent plastic (COC) syringe with luer lock.
- [0083] rubber tip cap, FM257/2 dark grey
- [0084] rubber plunger stopper, 1 ml long, 4023/50, Fluorotec B2-40

EXPERTS\_MYL\_002404  
PTX-115

PTX-0115\_0012

US 2009/0163519 A1

Jun. 25, 2009

9

[0085] 2.25 ml transparent plastic (COC) syringe with luer lock.

[0086] rubber tip cap, FM257/2 dark grey

[0087] rubber plunger stopper, 1-3 ml, 4023/50, Fluorotec B2-40

[0088] The empty syringes with pre-assembled tip-caps were sterilized by gamma-irradiation (dose  $\geq 25$  kGy). The rubber plunger stoppers were sterilized by means of steam sterilization ( $F_0 \geq 1$ ).

#### Example 2

Evaluation of the Pharmacokinetic Profile of Gluteal Versus Deltoid Intramuscular Injections of Paliperidone Palmitate 100 mg Equivalent in Patients with Schizophrenia

[0089] This study was performed to characterize and compare the pharmacokinetic profile of paliperidone palmitate (formulated as described above) following four intramuscular injections in the deltoid or gluteal muscle.

#### Method

[0090] In this multiple-dose, open-label, parallel-group study, patients with schizophrenia were randomized to receive four consecutive intramuscular injections (days 1, 8, 36 and 64) of paliperidone palmitate 100 mg-eq. administered into either the deltoid (n=24) or gluteal muscle (n=25). Plasma samples for pharmacokinetic analyses were collected. The total paliperidone concentration was calculated as the sum of both enantiomers.

#### Results

[0091] The median  $C_{max}$  for paliperidone was higher in the deltoid versus the gluteal muscle after the second (31.3 versus 24.1 ng/mL) and fourth (23.7 versus 22.3 ng/mL) injections. After four injections, median  $AUC_{\infty}$  was similar for both injection sites;  $C_{max}$  and  $AUC_{\infty}$  for paliperidone were 30% (90% CI=100.56%-168.93%) and 20% (90% CI=93.09%-154.69%) higher in deltoid versus gluteal muscle, respectively. Median  $T_{max}$  was similar between injection sites after the second (10 day versus 10 day) and fourth injections (5 versus 6.5 days). After four injections, the median peak-to-trough ratio was higher (2.3 versus 1.9), with a larger inter-subject variability for deltoid versus gluteal injection. An increase in median predose plasma concentration between days 8, 36 and 64 for both sites suggested subjects were not completely at steady state after four injections. Relative exposure after the fourth injection was slightly lower than after the second injection in both the deltoid and gluteal muscle. Most commonly reported adverse events (combined injection sites) were orthostatic hypotension (24%), hypotension (14%), diastolic hypotension (12%) and injection site pain (14%). There were four serious adverse events (worsening of psychosis) that led to discontinuations. There were no deaths in the study. Paliperidone palmitate was well tolerated with more favorable local tolerability profile in the gluteal versus deltoid; mean injection site pain VSA score was 3.3 for gluteal versus 10.8 for deltoid muscle (day 1, 8 hours after injection).

#### Conclusion

[0092] Paliperidone palmitate 100 mg-eq. injections resulted in an increased  $AUC_{\infty}$ , higher  $C_{max}$ , greater FI, but

similar  $T_{max}$  following four consecutive injections into the deltoid versus gluteal muscle. Paliperidone palmitate 100 mg-eq. was systemically and locally well tolerated in this study.

#### Example 3

Assessment of the Dose Proportionality of Paliperidone Palmitate 25, 50, 100, and 150 mg eq. Following Administration in the Deltoid or Gluteal Muscles

[0093] This study evaluated dose proportionality of paliperidone palmitate injections when administered into either the gluteal or deltoid muscle.

#### Method

[0094] A single-dose, open label, parallel-group study of 201 randomized schizophrenia subjects was performed. The subjects were assigned into eight treatment groups: paliperidone palmitate 25 (n=48), 50 (n=50), 100 (n=51) or 150 (n=52) mg-eq. injected into either the deltoid or gluteal muscle. Serial plasma samples were collected for pharmacokinetic evaluation over 126-day period. The total paliperidone concentration was calculated as the sum of both enantiomers. Dose proportionality was assessed by linear regression model, for each injection site, with log-transformed dose-normalized  $AUC_{\infty}$  and  $C_{max}$  as dependent variables and log-transformed dose as predictor, respectively of  $C_{max}$  and  $AUC_{\infty}$  ratios of the enantiomers were documented.

#### Results

[0095] Slopes for log-transformed dose-normalized  $AUC_{\infty}$  were not significantly different from zero for deltoid (slope -0.06; p=0.036) and gluteal injections (slope -0.02; p=0.760) indicating a dose-proportional increase in  $AUC_{\infty}$ .  $T_{max}$  was comparable between doses but slightly earlier for deltoid (13-14 days) versus gluteal injections (13-17 days). Median  $C_{max}$  was higher with deltoid (range 5.3-11.0 ng/mL) versus gluteal (range 5.1-8.7 ng/mL) injections except for the 100 mg-eq. deltoid (slope -0.22, p=0.0062) and gluteal (slope -0.31; p<0.0001) injections, indicating a less than dose-proportional increase in  $C_{max}$ . Results of  $C_{max}$  and  $AUC_{\infty}$  were confirmed using pairwise comparisons. Plasma concentrations of (+)-enantiomer were consistently higher than (-)-enantiomer; (+)/(-) plasma concentrations ratio was approximately 2.4 shortly after administration and decreased to ~1.7 for both injection sites, independent of dose. After a single dose of paliperidone palmitate, subjects received concomitant oral antipsychotics. Treatment-emergent AEs (TEAs) included tachycardia (10%), headache (7%), schizophrenia (6%), insomnia (5%). Only 2% of subjects discontinued due to TEAs. No deaths were reported.

#### Conclusion

[0096]  $AUC_{\infty}$  increased proportionality with increasing paliperidone palmitate doses (5-150 mg-eq.), regardless of gluteal or deltoid injection. Overall, deltoid injection was associated with a higher  $C_{max}$  (except for 100 mg-eq.) and slightly earlier  $T_{max}$  compared with gluteal injections.

#### Example 4

Comparison of the PK Profile in the Deltoid to that in the Gluteal

[0097] The plasma concentration-time profile of paliperidone after single i.m. injection of the paliperidone palmitate formulation at 25-150 mg-eq. has been documented in several studies (Table 4). Details of how the comparison of injection sites study and the dose proportionality studies were performed are provided in Examples 2 and 3.

EXPERTS\_MYL\_002405  
PTX-115

PTX-0115\_0013



US 2009/0163519 A1

10

Jun. 25, 2009

TABLE 4

Table of Clinical Studies Summarized	
Study	Design/Treatment/PK Objective
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-INT-12 (dose-proportionality)	S.D., OL, parallel group/single i.m. injection of F011*, 25, 50, 100 or 150 mg eq./document PK of the F011* formulation at different doses, enantiomer disposition
R092670-USA-3	M.D., OL, randomized, parallel groups/2 i.m. injections of R092670 (F011*) 25 or 150 mg eq., gluteal or deltoid, separated by 1 week/compare the PK after deltoid and gluteal injections, explore the relationship between R092670 PK parameters and CYP P450 genotypes
R092670-PSY-1001 (comparison of injection site)	M.D., OL, randomized, parallel groups/4 i.m. injections of R092670 (F013) 100 mg eq. in the gluteal or deltoid muscle (on Day 1, 8, 36 and 64)/compare the PK at steady state between deltoid and gluteal injection sites
R092670-PSY-1004 (dose-proportionality)	S.D., OL, randomized, parallel groups/single i.m. injection of R092670 (F013) 25, 50, 100 or 150 mg eq. in the gluteal or deltoid muscle/evaluate dose proportionality of F013 formulation over a dose range of 25-150 mg eq., compare the PK after deltoid and gluteal injections

S.D.: single dose; M.D.: multiple dose; OL: open-label; DB: double blind; PK: pharmacokinetic; PC: placebo-controlled; AC: active-controlled; pali ER: paliperidone extended release; pali IR: paliperidone immediate release  
F011\*: Sterilized by gamma-irradiation. Otherwise, sterilized by aseptic crystallization.

[0098] The total exposure ( $AUC_{\infty}$ ) of paliperidone increased proportionally with dose after single-dose injections of 25 to 150 mg eq. paliperidone palmitate in both the deltoid and gluteal muscle. The increase in  $C_{max}$  was slightly less than dose proportional for both injections sites at doses greater than 50 mg eq. The apparent half-life (reflecting the absorption rate for this type of formulations) increased with dose from 25 days (median) after the 25 mg eq. dose to 40-49 days (median) after the 100 and 150 mg eq. dose, for both injection sites. The  $C_{max}$  of paliperidone was generally higher after single-dose injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (geometric mean ratio ranging from 108.75% to 164.85%) whereas this was much less pronounced for  $AUC_{\infty}$  (geometric mean ratio ranging from 103.00% to 117.83%). The median apparent half-life was comparable between injection sites.

## Example 5

## Description of the PK Profile in the Gluteal After Multiple Administrations

[0099] Paliperidone palmitate is a long-acting i.m. injectable, intended to release over a period of 1 month. In order to attain this long injection interval, an ester of paliperidone was prepared that has a limited solubility in a physiological environment. The ester was subsequently formulated as an aqueous suspension for i.m. injection. The rate of dissolution is governed by the particle size distribution whereby it was experimentally determined that an optimal particle size range is contained within xx-yy microm ( $d_{50v}$ ). In fact, the rate of dissolution (and thus the particle size distribution) fully determines the in vivo behaviour, as was nicely demonstrated in study PSY-1002. It was found that the median  $C_{max}$  increases and  $t_{max}$  shortens with decreasing particle size, which is consistent with the hypothesis that particle size is driving the release rate. The point estimates suggest that paliperidone exposure ( $AUC$ ,  $C_{max}$ ) after injection of paliperidone palmitate is similar between the to-be-marketed formulation F013 and formulation F011.

TABLE 5

Table of Clinical Studies Summarized in Module 2.7.2	
Study	Design/Treatment/PK Objective
PHASE 1 STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-BEL-4 (pilot, dose-proportionality)	M.D., OL, sequential, parallel groups/4-6 monthly i.m. injections of F004, 50 mg eq. or 100 mg eq. or 150 mg eq./explore M.D. PK and dose-proportionality
R092670-BEL-7 (dosing regimen)	M.D., OL, parallel groups/F004 formulation: Panel I: 100 mg eq. i.m. followed by 3 monthly i.m. injections of 50 mg eq.; Panel II: 200 mg eq. i.m. followed by 3 monthly i.m. injections of 100 mg eq.; Panel III: 300 mg eq. i.m. followed by 3 monthly i.m. injections of 150 mg eq.; Panel IV: 50 mg eq. i.m. followed by 1 week later by 4 monthly i.m. injections of 50 mg eq.; Panel V: 150 mg eq. i.m. followed by 1 week later by 4 monthly i.m. injections of 150 mg eq./explore the M.D. PK with various dosing regimens

EXPERTS\_MYL\_002406  
PTX-115

PTX-0115\_0014

US 2009/0163519 A1

Jun. 25, 2009

11

TABLE 5-continued

Table of Clinical Studies Summarized in Module 2.7.2	
Study	Design/Treatment/PK Objective
PHASE I STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R092670-INT-11 (compare F004 and F011)	M.D., DB, randomized, 4-group 2-way cross-over/4 monthly i.m. injections of F004 or F011*, 2 x 50 and 2 x 150 mg eq./compare PK of F004 and F011* formulations; compare S.D. and M.D. PK of both formulations
R092670-PSY-1002 (IVIVC)	S.D., OL, randomized, parallel groups/single i.m. injections of 1 mg paliperidone IR, followed by single i.m. injection of 50 mg eq. R092670: 1 of 4 F013 formulations with different particle sizes, or F011 formulation with medium particle size/explore IVIVC of 4 F013 formulations, compare the PK of F011 and F013 formulations
R092670-PSY-1001 (comparison of injection site)	M.D., OL, randomized, parallel groups/4 i.m. injections of R092670 (F013) 100 mg eq. in the gluteal or deltoid muscle (on Day 1, 8, 36 and 64)/compare the PK at steady state between deltoid and gluteal injection sites

S.D.: single dose; M.D.: multiple dose; OL: open-label; DB: double blind; PK: pharmacokinetic; PC: placebo-controlled; AC: active-controlled; paliperidone extended release; paliperidone immediate release  
F011\*: Sterilized by gamma-irradiation. Otherwise, sterilized by aseptic crystallization.

[0100] Pharmacokinetic theory also implies that for a formulation with such a long apparent half-life it takes 4-5 times this half-life for steady-state to be achieved. For individual patients, this means that following the first few injections, only subtherapeutic plasma concentrations are achieved. In order to overcome this problem, a loading dose regimen was developed (BEL-7), that was subsequently used in phase 2 and 3 of drug development. The dosing regimen consisting of two initial i.m. injections separated by one week followed by subsequent doses at monthly intervals resulted in a faster attainment of apparent steady state compared with a dosing regimen of one initial injection of twice the monthly dose followed by subsequent doses at monthly intervals. Somewhat higher peak-to-through fluctuations were observed with the first dosing regimen as compared with the latter one. The dosing regimen consisting of two initial i.m. injections separated by one week followed by subsequent doses at monthly intervals was selected for further studies and is also the recommended regimen for treatment.

#### Example 6

##### Description of the Exposure Range Needed for Efficacy Using Invega Data

[0101] All antipsychotic drugs currently on the market have one feature in common: they antagonize the  $D_2$  receptor at the level of the brain. It has been empirically derived and is currently widely accepted that 65-70% occupancy is needed for antipsychotics to show clinical efficacy (Farde et al.), i.e. improvement on the PANSS scale. A too high occupancy (80-85%) will typically increase the risk to develop EPS. In order to determine the central  $D_2$  occupancy, PET trials in human healthy volunteers are typically performed. Two such studies have been done for paliperidone: SWE-1 and SIV-101, showing that the  $K_D^{app}$  for  $D_2$  occupancy was ranging from 4.4 to 6.4 ng/mL. Using the 65-85% occupancy window, it can be calculated that the exposure range for efficacy without an increased risk to develop EPS as compared to placebo (<5% difference in probability) is contained in the window of 7.5-40 ng/mL.

[0102] In addition, based on the results of the phase 3 program of 6 mg paliperidone ER, in which plasma samples

were collected at several time points, a plasma concentration of 7.5 ng/mL was identified as the cut-off value above which 90% of the plasma concentrations were observed. The risk to develop EPS was clearly higher for dose above 9 mg Invega. Calculating back, this roughly corresponds to an exposure level of 35-40 ng/mL at steady-state. This implies that there is ample evidence to support a target exposure efficacy range of 7.5-40 ng/mL. This should be the target exposure range for paliperidone after injection of the paliperidone palmitate formulation.

#### Example 7

##### Optimal Way of Dosing

[0103] During the development of paliperidone palmitate, as the result of an extensive population PK analysis (refer to popPK report for paliperidone palmitate), several factors were found to slow down the release of paliperidone from the formulation, resulting in a slower build-up of plasma concentrations at the start of therapy and in more time required to reach steady-state. One factor was body mass index: the higher the BMI, the slower the dissolution (probably related to local physiological factors such as diminished blood flow at the site of injection); the other one being volume administered: the higher the volume injected, the slower the dissolution (probably related to the nonlinear relationship between surface area and volume). This has resulted in a lower than expected exposure using the originally proposed loading dose regimen, and the need to come up with an improved loading dose scheme for all patients irrespective of BMI in order to avoid drop-out due to lack of efficacy at the start of therapy. The aim was to get patients as quickly as possible above the 7.5 ng/mL, certainly after 1 week for all doses considered (25 mg-eq. and above).

[0104] Simulation scenarios with the statistically significant covariates from the population PK analysis revealed the following features about the paliperidone PK after injection of paliperidone palmitate:

[0105] Compared to deltoid injections, repeated administration in the gluteal muscle resulted in a delayed time to achieve steady-state (~4 wk longer), but did not influ-

EXPERTS\_MYL\_002407  
PTX-115

PTX-0115\_0015

US 2009/0163519 A1

Jun. 25, 2009

12

ence the overall exposure (in terms of steady-state concentrations) to paliperidone.

[0106] Deltoid injections resulted in a faster rise in initial plasma concentrations, facilitating a rapid attainment of potential therapeutic plasma concentrations. The deltoid injection site is therefore recommended as the initiation site for dosing paliperidone palmitate.

[0107] Higher doses, associated with larger injection volumes, increased the apparent half-life of paliperidone, which in turn increased the time to achieve steady-state.

[0108] Needle length was an important variable for the absorption kinetics from the deltoid injection-site and it is recommended to use a longer 1.5-inch needle for deltoid administration in heavy subjects ( $\geq 90$  kg). Simulations indicated that the use of a longer needle in the deltoid muscle for the heavy individuals might be associated with an initial faster release of paliperidone into the systemic circulation, which could help overcome the slower absorption observed in heavier individuals described below.

[0109] The body size variable BMI was another important covariate for paliperidone palmitate. A slower rise in initial concentrations was observed in the obese population, which possibly occurred due to the reduced speed of initial influx from the injection site. Initiating the first two injections in the deltoid muscle and using a longer 1.5-inch needle for deltoid injection in heavy subjects can mitigate this effect. These observations are consistent with the expectation that in heavy subjects, administration into the adipose layer of the deltoid muscle can be avoided with the use of a longer injection needle.

Summarize what the optimized loading dose regimens would be here:

[0110] 150 deltoid (day 1), 100 mg deltoid (day 8), then every 4 weeks maintenance (gluteal or deltoid) (PSY-3006, simulations—popPK report palmitate)

[0111] 100 deltoid (day 1), 100 mg deltoid (day 8), then every 4 weeks maintenance (gluteal or deltoid) (simulations—popPK report palmitate, proposed for the label)

[0112] 150 mg deltoid day 1, maintenance dose day 8 and then every 4 weeks (gluteal or deltoid) (PSY-3007)

#### Example 8

[0113] TITLE OF STUDY: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Doses (25 mg eq., 100 mg eq., and 150 mg eq.) of Paliperidone Palmitate in Subjects With Schizophrenia

Phase of Development: Phase 3

[0114] OBJECTIVES: The primary objectives of this study were to evaluate the efficacy and safety of 3 fixed doses of paliperidone palmitate administered intramuscularly (i.m.) after an initial dose of 150 mg equivalent (eq.) in the deltoid muscle followed by either deltoid or gluteal injections for a total of 13 weeks of treatment as compared with placebo in subjects with schizophrenia. The secondary objectives were to:

[0115] Assess the benefits in personal and social functioning (key secondary endpoint) associated with the use of paliperidone palmitate compared with placebo;

[0116] Assess the global improvement in severity of illness associated with the use of paliperidone palmitate compared with placebo;

[0117] Assess the dose-response and exposure-response relationships of paliperidone palmitate.

[0118] METHODS: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-response study of men and women, 18 years of age and older, who had a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia. The study included a screening period of up to 7 days and a 13-week double-blind treatment period. The screening period included a washout of disallowed psychotropic medications.

[0119] Subjects without source documentation of previous exposure to at least 2 doses of oral risperidone or paliperidone extended-release (ER), at least 1 dose of i.m. RISPERDAL® CONSTA® or paliperidone palmitate, or who were not currently receiving an antipsychotic medication were given 4 to 6 days of paliperidone ER 6 mg/day (or the option of oral risperidone 3 mg/day for subjects in Malaysia) for tolerability testing. Subjects who had source documentation of previous exposure to the above medications and were currently taking another antipsychotic regimen continued their current treatment through Day-1. At the beginning of the double-blind treatment period, subjects were randomly assigned in a 1:1:1:1 ratio to 1 of 4 treatment groups: placebo or paliperidone palmitate 25 mg eq., 100 mg eq., or 150 mg eq. Study medication was administered as 4 doses: an initial i.m. injection of 150 mg eq. of paliperidone palmitate or placebo followed by 3 fixed i.m. doses of placebo or paliperidone palmitate [25, 100, or 150 mg eq.] on Days 8, 36, and 64. The initial injection of study medication was given in the deltoid muscle. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during the double-blind period. The entire study, including the screening period, lasted approximately 14 weeks. Samples for pharmacokinetic (PK) evaluation were collected on Day 1, prior to the first injection and on Days 2, 4, 6, 8, 15, 22, 36, 64 and 92. Efficacy and safety were evaluated regularly throughout the study. A pharmacogenomic blood sample (10 mL) was collected from subjects who gave separate written informed consent for this part of the study. Participation in the pharmacogenomic research was optional. Approximately 105 to 115 mL of whole blood was collected during the study.

[0120] Number of Subjects (Planned and Analyzed): It was planned to include approximately 644 men and women in this study. A total of 652 eligible subjects from 72 centers in 8 countries were randomized and received at least 1 dose of double-blind study medication (safety analysis set); 636 subjects had both baseline and post baseline efficacy data (intent-to-treat analysis set).

[0121] Diagnosis and Main Criteria for Inclusion: Male or female subjects  $\geq 18$  years of age who met the DSM-IV diagnostic criteria for schizophrenia for at least 1 year before screening, had a Positive and Negative Syndrome Scale (PANSS) total score at screening of between 70 and 120, inclusive, and at baseline of between 60 and 120, inclusive, and had a body mass index (BMI) of  $>17.0$  kg/m<sup>2</sup> to  $<40$  kg/m<sup>2</sup> were eligible.

[0122] Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER was supplied as a 6-mg capsule-

EXPERTS\_MYL\_002408  
PTX-115

PTX-0115\_0016



US 2009/0163519 A1

Jun. 25, 2009

13

shaped tablet for the oral tolerability test (batch number 0617714/F40). Paliperidone palmitate was supplied as 25, 100, or 150 mg eq. injectable suspension (batch numbers 06K22/F13 and 07D23/F13). For the oral tolerability test, a 6-mg tablet of paliperidone ER (or the option of oral risperidone 3 mg/day for subjects in Malaysia) was administered daily for 4 to 6 days. On Day 1 of the double-blind treatment period, 150 mg eq. of paliperidone palmitate was injected in the deltoid muscle followed by 25, 100, or 150 mg eq. i.m. injections of paliperidone palmitate on Days 8, 36, and 64, injected into the deltoid or gluteal muscle at the investigator's discretion.

[0123] Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as 20% Intralipid (200 mg/mL) injectable emulsion (batch numbers 06K14/F00 and 07F12/F00). An injection was given on Days 1, 8, 36 and 64.

[0124] Duration of Treatment: The study consisted of a screening and washout phase of 7 days and a double-blind treatment period of 13 weeks, starting with the first injection in the deltoid muscle followed by a second injection 1 week later. All injections after Day 1 were given in either the deltoid or the gluteal muscle at the discretion of the investigator. Two subsequent injections were given at 4-week intervals.

#### Criteria for Evaluation:

[0125] Pharmacokinetic Evaluations: A sparse blood sampling procedure was followed to study the paliperidone concentration-time profiles. Paliperidone plasma concentration-time data were subject to population PK analysis using nonlinear mixed-effects modeling, and details are described in a separate report.

[0126] Efficacy Evaluations/Criteria: The primary endpoint was the change in the PANSS total score from baseline (i.e., the start of double-blind treatment, Day 1) to the end of the double-blind treatment period (i.e., Day 92 or the last post baseline assessment). The key secondary efficacy endpoint was the change in the Personal and Social Performance Scale (PSP) from baseline to the end of the double-blind treatment period. The other secondary efficacy endpoint was the change in the Clinical Global Impression-Severity (CGI-S) scores from baseline to the end of the double-blind treatment period. Other endpoints included the change from baseline in subject ratings of sleep quality and daytime drowsiness using a visual analogue scale (VAS), the onset of therapeutic effect, responder rate, and the change from baseline to end point in PANSS subscales and Marder factors.

[0127] Safety Evaluations: Safety was monitored by the evaluation of adverse events, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], Simpson and Angus Rating Scale [SAS]) scores, clinical laboratory test results, vital signs measurements, electrocardiograms (ECGs), and physical examination findings. In addition, the tolerability of injections was assessed; the investigators evaluated injection sites and the subjects assessed injection pain.

[0128] STATISTICAL METHODS: All randomized subjects who received at least 1 dose of double-blind study drug and had both baseline and at least one post baseline efficacy measurement (PANSS, PSP, or CGI-S) during the double-blind treatment period were included in the intent-to-treat efficacy analyses. The overall type 1 error rate for testing all paliperidone palmitate doses versus placebo for both the primary endpoint (change in PANSS total score at end point) and

the key secondary efficacy endpoint (change in PSP total score at end point) was controlled at the 2-sided 0.05 significance level. The 2 families of hypotheses (in each family, 3 comparisons for each of the paliperidone palmitate doses versus placebo) were tested using a parallel gatekeeping procedure that adjusts for multiplicity using Dunnett's method in each family of hypotheses and using Bonferroni's inequality between different families of hypotheses. This procedure is referred to as the Dunnett-Bonferroni-based parallel gatekeeping procedure.

[0129] The change from baseline in PANSS total score at each visit and at end point was analyzed using an analysis of covariance (ANCOVA) model. The last observation carried forward (LOCF) method was used. The model included treatment and country as factors and baseline PANSS total score as a covariate. Treatment effect was based on the difference in least-squares mean change. Dunnett's test was used to adjust for multiple comparisons of the 3 paliperidone palmitate dosages versus placebo. Unadjusted 2-sided 95% confidence intervals were presented for the difference in least-squares mean change of each paliperidone palmitate dosage group compared with placebo. Treatment-by-country and treatment-by-baseline PANSS total score interactions were explored using the same ANCOVA model as the one for the analysis of the primary endpoint. If either term was statistically significant at the predefined 2-sided significance level of 0.10, further evaluations of the effect of other covariates were to be performed to assess the nature of the interaction and identify possible causes. In addition, to address the dose-response relationship and to facilitate the discussion of dosage selection, an analysis to compare the 3 active paliperidone palmitate dosages with each other was performed without adjustment for multiple comparisons.

[0130] The analysis of the key secondary endpoint, change in PSP score at end point, was conducted by means of an ANCOVA model with treatment and country as factors and the baseline score as the covariate. The Dunnett-Bonferroni-based parallel gatekeeping approach was used to adjust for multiple testing.

[0131] Between-group comparisons of CGI-S were performed by using an ANCOVA model on the ranks of change from baseline, with treatment and country as factors and the baseline score as the covariate.

[0132] Change from baseline over time (observed case) in the PANSS total score was explored using mixed effects linear models for repeated measures with time, treatment, country, and treatment-by-time as factors and baseline score as a covariate.

[0133] The number and percentage of subjects with treatment-emergent adverse events were summarized. Adverse events of potential clinical interest were summarized separately, including events related to EPS or changes in serum glucose or prolactin levels.

[0134] Changes from baseline in clinical laboratory tests, vital sign measurements, ECGs, body weight, BMI, and EPS scale scores were summarized by treatment group. Prolactin levels were summarized by sex. Subjects with potentially abnormal values or changes in clinical laboratory tests, vital signs, orthostatic parameters, and ECG parameters were summarized based on predefined criteria. Frequency distributions were presented for the investigator's evaluation of the injection.

EXPERTS\_MYL\_002409  
PTX-115

PTX-0115\_0017



US 2009/0163519 A1

Jun. 25, 2009

14

tion site, and descriptive statistics were presented for VAS scores corresponding to the subject's evaluation of injection pain.

#### Results:

**[0135]** The majority of subjects in the paliperidone palmitate treatment groups (56%-61%) received all 4 injections compared with 48% of the placebo-treated subjects. Completion rates were also higher for the paliperidone palmitate groups (52%-55%) than for the placebo group (43%). More subjects were discontinued for lack of efficacy in the placebo group (27%) compared with the paliperidone palmitate groups (14%-19%).

**[0136]** Demographic and Baseline Characteristics: The double-blind treatment groups were well matched with respect to demographic and baseline disease characteristics and psychiatric history. The 636 subjects who comprised the intent-to-treat analysis set were mainly male (67%), racially diverse (54% White, 30% Black, 14% Asian, 1% other races), and predominately between the ages of 26 and 50 years (75%). Most subjects had a primary diagnosis of paranoid schizophrenia (88%), and were highly symptomatic as indicated by a mean PANSS total score of 87.1 at baseline. There were notable differences between countries with respect to BMI and gender, with subjects enrolled at centers in the U.S. being more likely to be male and obese (i.e., BMI  $\geq 30$  kg/m<sup>2</sup>) than those from centers in other countries.

**[0137]** Pharmacokinetics: A total of 488 subjects who were randomly assigned to receive paliperidone palmitate treat-

peridone plasma concentrations on Day 8 were lower in subjects with high BMI ( $\geq 25$  to  $<30$  kg/m<sup>2</sup> and  $\geq 30$  kg/m<sup>2</sup>; overweight/obese) compared to subjects with low BMI ( $<25$  kg/m<sup>2</sup>) for the 3 dose groups. After Day 8, no consistent trends were observed for the 3 paliperidone palmitate dose groups with respect to paliperidone plasma concentrations as a function of baseline BMI classification.

**[0138]** The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. treatment group were approximately 2-fold higher than those for the 25 mg eq. treatment group. Thus, the PK profile for the 25 mg eq. and 100 mg eq. dose groups appeared to be less than dose proportional, which is the result of the initial paliperidone palmitate 150 mg eq. injection on Day 1 in all active treatment groups. The mean and median paliperidone plasma concentrations on Day 64 for the 100 mg eq. dose were apparently dose proportional compared to the 150 mg eq. dose. A high inter-subject variability was observed in the paliperidone plasma concentrations on Days 1 and 2 with a % CV of 118.9% (Day 1) and 153.1% (Day 2). After Day 2, the inter-subject variability decreased and the % CV ranged from 50.4 to 83.4%.

**[0139]** Primary Efficacy Analysis: Adult subjects with schizophrenia achieved statistically significant improvements in the PANSS total score (primary efficacy endpoint) with all 3 doses of paliperidone palmitate compared to placebo (25 mg eq.:  $p=0.034$ ; 100 mg eq.:  $p<0.001$ ; 150 mg eq.:  $p<0.001$ ) based on the intent-to-treat LOCF analysis and the Dunnett's test to control for multiplicity.

Positive and Negative Syndrome Scale for Schizophrenia (PANSS)  
Total Score - Change from Baseline to End Point-LOCF with the  
Dunnett-Bonferroni-Based Parallel Gatekeeping Procedure  
(Study R092670-PSY-3007: Intent-to-Treat Analysis Set)

	Placebo (N = 160)	R092670 25 mg eq. (N = 155)	R092670 100 mg eq. (N = 161)	R092670 150 mg eq. (N = 160)
Baseline Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)
End point Mean (SD)	83.9 (21.44)	78.8 (19.88)	74.6 (18.06)	75.2 (18.59)
Change from Baseline				
Mean (SD)	-2.9 (19.26)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
P-value (minus Placebo) <sup>a</sup>		0.034	<0.001	<0.001
Diff of LS Means (SE)		-5.1 (2.01)	-8.7 (2.00)	-9.8 (2.00)

<sup>a</sup>Based on analysis of covariance (ANCOVA) model with treatment (Placebo, R092670 25 mg eq., R092670 100 mg eq., R092670 150 mg eq.) and country as factors, and baseline value as a covariate. P-values were adjusted for multiplicity for comparison with placebo using Dunnett's test.

Note:  
Negative change in score indicates improvement.

ment had scheduled pharmacokinetic blood samples taken over the course of the study. The median paliperidone predose concentration for the 25 mg eq. treatment group was highest on Day 8, which is the result of the initial 150 mg eq. dose on Day 1. After Day 8, paliperidone concentrations decreased and seemed to reach steady state levels on Day 92 based on visual inspection. The median paliperidone predose concentration for the 100 mg eq. treatment group remained in the same range from Day 8 onwards. The median predose concentration for the 150 mg eq. treatment group seemed to increase up to the last study day, Day 92. The median paliperidone

**[0140]** Other Efficacy Results: There was a dose-response pattern with respect to the primary efficacy variable, with the mean decreases (improvement) in the PANSS total score at end point (LOCF).

**[0141]** Prespecified treatment-by-country and treatment-by-baseline PANSS total score interactions in the primary efficacy model were not statistically significant at the 0.10 level. An exploratory analysis additionally provided no statistical evidence for a BMI effect on treatment.

**[0142]** All 3 paliperidone palmitate dose groups showed a statistically significant improvement over placebo in the

EXPERTS\_MYL\_002410  
PTX-115

PTX-0115\_0018

US 2009/0163519 A1

Jun. 25, 2009

15

change in PANSS total score as of Day 22 and at every subsequent time point, and as early as Day 8 in the paliperidone palmitate 25 mg eq. and 150 mg eq. groups.

[0143] The mean improvements in the PSP score from baseline to end point, the key secondary efficacy outcome measure, showed a dose response among the 3 paliperidone palmitate groups (25 mg eq.: 2.9; 100 mg eq.: 6.1; 150 mg eq.: 8.3); all were numerically higher than the mean improvement

injections at fixed doses of 25 mg eq., 100 mg eq., or 150 mg eq. on Days 8, 36, and 64, was generally well tolerated by adult subjects with schizophrenia during this 13-week study. Overall, the safety and tolerability results were consistent with previous clinical studies involving paliperidone palmitate, and no new safety signals were detected.

[0148] The overall summary of treatment-emergent adverse events is given below.

Overall Summary of Treatment-Emergent Adverse Events (Study R092670-PSY-3007: Safety Analysis Set)					
	Placebo (N = 164) n (%)	R092670 25 mg eq. (N = 160) n (%)	R092670 100 mg eq. (N = 165) n (%)	R092670 150 mg eq. (N = 163) n (%)	Total (N = 652) n (%)
TEAE	107 (65.2)	101 (63.1)	99 (60.0)	103 (63.2)	410 (62.9)
Possibly related TEAE*	47 (28.7)	45 (28.1)	49 (29.7)	51 (31.3)	192 (29.4)
TEAE leading to death	0	0	0	1 (0.6)	1 (0.2)
1 or more serious TEAE	23 (14.0)	15 (9.4)	22 (13.3)	13 (8.0)	73 (11.2)
TEAE leading to permanent stop	11 (6.7)	10 (6.3)	10 (6.1)	13 (8.0)	44 (6.7)

\*Study drug relationships of possible, probable, and very likely are included in this category.  
Adverse events are coded using MedDRA version 10.1

in the PSP score seen in the placebo group (1.7). Based on the intent-to-treat LOCF analysis of this key secondary efficacy variable, using the Dunnett-Bonferroni-based parallel gate-keeping procedure to adjust for multiplicity, the improvement in the paliperidone palmitate 100 and 150 mg eq. treatment groups reached statistical significance (100 mg eq.:  $p=0.007$ ; 150 mg eq.:  $p<0.001$ ) when compared with the placebo group.

[0144] The paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significantly superior to placebo in improving the CGI-S scores from baseline to end point (LOCF) (without multiplicity adjustment, 100 mg eq.:  $p=0.005$ ; 150 mg eq.:  $p<0.001$ ). Significantly more subjects treated with paliperidone palmitate 25 mg eq. (33.5%;  $p=0.007$ ), 100 mg eq. (41.0%;  $p<0.001$ ), and 150 mg eq. (40.0%,  $p<0.001$ ) achieved responder status (30% or larger decrease on PANSS total scores) than with placebo (20.0%).

[0145] Based on the intent-to-treat LOCF analysis of the change from baseline to end point without statistical adjustment for multiplicity, the paliperidone palmitate 100 and 150 mg eq. groups were statistically significantly superior to the placebo group for all 5 PANSS Marder factors ( $p<0.010$ ). The improvements in both negative symptoms and disorganized thoughts factor scores were statistically significantly greater in the paliperidone palmitate 25 mg eq. group compared with placebo ( $p=0.032$ ).

[0146] Based on the intent-to-treat LOCF analysis using an ANCOVA model with no adjustment for multiplicity, the mean improvement in sleep quality in the paliperidone palmitate 100 mg eq. and 150 mg eq. groups were statistically significant ( $p<0.001$  and  $p=0.026$ , respectively) when compared with placebo. The mean changes in daytime drowsiness in the paliperidone palmitate treatment groups were not statistically significantly different from that in the placebo group (25 mg eq.:  $p=0.541$ ; 100 mg eq.:  $p=0.340$ ; 150 mg eq.:  $p=0.261$ ).

[0147] Safety Results Paliperidone palmitate, injected at a dose of 150 mg eq. into the deltoid muscle followed by 3 i.m.

[0149] There was 1 death in a subject in the paliperidone palmitate 150 mg eq. group after withdrawal from the study due to an adverse event (cerebrovascular accident) that began during the study. This subject received 2 injections of study medication, with the last injection administered approximately 2 weeks before the subject died. While this event was assessed as doubtfully related to study treatment by the investigator, an unblinded review by the sponsor assessed this event to be possibly related to study treatment.

[0150] The number of subjects who experienced treatment-emergent serious adverse events was higher in the placebo group than in any of the paliperidone palmitate groups (see table above). Most serious adverse events in all treatment groups were psychiatric disorders (e.g., schizophrenia, psychotic disorder) that were likely the result of the natural course of the underlying schizophrenia. Adverse events leading to study discontinuation occurred at a similar low incidence across treatment groups.

[0151] Common treatment-emergent adverse events ( $\geq 2\%$  of subjects in any treatment group) that occurred more frequently in the total paliperidone palmitate group (all 3 active dose groups combined) than in the placebo-treated subjects (i.e.,  $\geq 1\%$  difference between the combined paliperidone palmitate group and the placebo group) were: injection site pain, dizziness, sedation, pain in extremity, and myalgia. An examination of treatment-emergent adverse events of potential clinical importance revealed no reports of seizure or convulsion, tardive dyskinesia, dermatologic events, neuroleptic malignant syndrome, hyperthermia, anaphylactic reaction, rhabdomyolysis, syndrome of inappropriate secretion of antidiuretic hormone, ventricular tachycardia, ventricular fibrillation, or torsades de pointes.

[0152] In general, the type and incidence of treatment-emergent adverse events did not differ as a function of baseline BMI categories (normal:  $<25 \text{ kg/m}^2$ ; overweight:  $\geq 25$  to  $<30 \text{ kg/m}^2$ ; obese:  $\geq 30 \text{ kg/m}^2$ ).

[0153] The incidence of treatment-emergent EPS-related adverse events was low and comparable to placebo. Akathisia

EXPERTS\_MYL\_002411  
PTX-115

PTX-0115\_0019

US 2009/0163519 A1

Jun. 25, 2009

16

was the most frequently reported EPS-related adverse event (4.9% for the placebo group and 1.3%, 4.8%, 5.5% for the paliperidone palmitate 25, 100, and 150 mg eq. groups, respectively). None of the EPS-related adverse events reported in subjects receiving paliperidone palmitate were serious or treatment limiting, and only 1 was severe (musculoskeletal stiffness). Results of EPS rating scales and use of anti-EPS medication were consistent in indicating that paliperidone palmitate was associated with a low incidence of EPS.

[0154] No clinically relevant mean changes from baseline to end point in supine or standing pulse rates were apparent for any of the paliperidone palmitate doses. A similar, low percentage of subjects had pulse rate of  $\geq 100$  bpm with an increase of  $\geq 15$  bpm in the placebo and paliperidone palmitate groups (6% to 11% for standing measurements; 2% to 5% for supine measurements).

[0155] Assessment of ECG data did not demonstrate evidence of clinically significant QTc prolongation with paliperidone palmitate at doses up to 150 mg eq. No subject had a maximum QTcLD value  $>480$  ms or a maximal change in QTcLD  $>60$  ms during the study.

[0156] The increases in body weight with paliperidone palmitate over the 13-week double-blind treatment period were modest in a dose-related manner, averaging 0.4, 0.7, and 1.4 kg for the 25 mg eq., 100 mg eq., and 150 mg eq. groups, respectively ( $-0.2$  kg for placebo); corresponding mean changes in BMI from baseline to end point were 0.1, 0.3, and 0.5 kg/m<sup>2</sup>, respectively ( $-0.1$  kg/m<sup>2</sup> for placebo). A clinically relevant weight increase of at least 7% relative to baseline was seen in 13% of subjects receiving the highest dose of paliperidone palmitate (compared with 5% for placebo).

[0157] Consistent with the known pharmacology of paliperidone, increases in prolactin levels were observed with greater frequency in subjects who received paliperidone palmitate, with the largest increase seen in the 150 mg eq. group. Overall, there was a low incidence of potentially prolactin-related adverse events, despite the known propensity of paliperidone palmitate to increase serum prolactin levels. This suggests that the clinical importance of this increase in serum prolactin levels is of questionable clinical significance.

[0158] Based on mean changes from baseline to end point and the occurrence of treatment-emergent markedly abnormal laboratory test values and adverse events related to abnormal laboratory analyte findings, except for prolactin, the effects of paliperidone palmitate on the results of chemistry and hematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not show clinically relevant differences from those of placebo.

[0159] Local injection site tolerability was good. Occurrences of induration, redness, or swelling as assessed by blinded study personnel were infrequent, generally mild, decreasing over time, and similar in incidence for the paliperidone palmitate and placebo groups. Investigator ratings of injection pain were similar for the placebo and paliperidone palmitate groups.

[0160] STUDY LIMITATIONS: This study investigated the efficacy and safety of paliperidone palmitate for acute treatment of schizophrenia over 13 weeks and does not provide information on longer term treatment. The study was not designed to detect differences between doses of paliperidone palmitate; thus, dose-related trends in efficacy and safety can only be described descriptively. The study was also not designed to demonstrate efficacy for specific subgroups of

subjects, such as those from a particular country. An independent, centralized blinded rating service was used for performing all ratings of PANSS, PSP and CGI-S for all subjects enrolled at U.S. sites. The investigators at these sites did not complete any of the ratings, which would have provided a reference for ratings provided by the rating service. Thus, data from this study cannot be used to fully evaluate the utility of using blinded independent raters for detecting treatment differences.

[0161] CONCLUSION: All 3 doses of paliperidone palmitate tested in this study—25, 100, and 150 mg eq.—were efficacious in adult subjects with schizophrenia who were experiencing acutely exacerbated schizophrenia. Specifically, the results of the primary efficacy endpoint (change from baseline to end point in PANSS total score) demonstrated statistical superiority of paliperidone palmitate 25 mg eq., 100 mg eq., and 150 mg eq. over placebo. Significantly greater improvement in subjects' personal and social functioning (as measured by the PSP score) was also seen for the paliperidone palmitate 100 mg eq. and 150 mg eq. doses compared with placebo, and global improvement was validated by a favorable and statistically significant CGI-S change for these 2 dose groups. There was a dose response in the primary and secondary efficacy endpoints (PANSS, PSP, and CGI-S). All 3 doses of paliperidone palmitate, including the highest dose of 150 mg eq., were well tolerated, suggesting a positive benefit-risk ratio across the dose range currently studied. No new safety signal was detected.

#### FIGURES

[0162] FIGS. 1-3 graphically presents the observed versus population pharmacokinetics model simulation for plasma paliperidone concentrations. The line indicates the median values calculated from population pharmacokinetic simulation. The shading indicates 90% prediction interval representing the between and within subject, variability obtained using the population pharmacokinetic simulation. The circles indicate observed plasma paliperidone concentrations. The arrows indicate the days when paliperidone palmitate injection was given. As is apparent from the Figures the plasma profiles provided by initiating paliperidone with 150 mg eq. followed by a subsequent dose of 100 or 150 for days 1-36 provide a rapid rise to a therapeutic dose levels. Most preferably the dosing of paliperidone to patients should be maintained within  $\pm 25\%$ , preferably 20% of the median plasma concentrations provided in these figures for days 1-36. For patients whose dosing continues at 100 mg eq. the preferably the dosing of paliperidone to patients should be maintained within  $\pm 25\%$ , preferably 20% of the median plasma concentrations provided in FIG. 2 for days 1-64. For patients whose dosing continues at 150 mg eq. the preferably the dosing of paliperidone to patients should be maintained within  $\pm 25\%$ , preferably 20% of the median plasma concentrations provided in FIG. 3 for days 1-64.

We claim:

1. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

(1) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

(2) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of

EXPERTS\_MYL\_002412  
PTX-115

PTX-0115\_0020



US 2009/0163519 A1

Jun. 25, 2009

17

- from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6<sup>th</sup> to about 10th day of treatment; and
- (3) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.
2. The method of claim 1 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30<sup>th</sup> day of treatment.
3. The method of claim 1 wherein the sustained release formulation is an aqueous nanoparticle suspension.
4. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising
- (a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
  - (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 100 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and
  - (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.
5. The method of claim 4 wherein the sustained release formulation is an aqueous nanoparticle suspension.
6. The method of claim 4 wherein the first loading dose is 150 mgs-eq. of paliperidone as paliperidone palmitate.
7. The method of claim 4 wherein the first loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.
8. The method of claim 4 wherein the second loading dose is 150 mg-eq. of paliperidone as paliperidone palmitate.
9. The method of claim 4 wherein the second loading dose is 100 mg-eq. of paliperidone as paliperidone palmitate.
10. The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg-eq. of paliperidone as paliperidone palmitate.
11. The method of claim 4 wherein the first loading dose and the second loading dose are 150 mg of paliperidone as paliperidone palmitate.
12. The method of claim 4 wherein the psychiatric patient is in need of treatment for psychosis.
13. The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.
14. The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.
15. The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Atten-

tion-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxi-

EXPERTS\_MYL\_002413  
PTX-115

PTX-0115\_0021

US 2009/0163519 A1

Jun. 25, 2009

18

olytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

17. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

- (a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6<sup>th</sup> to about 10th day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance

dose of about 25 mg-eq. to about 75 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

18. The method of claim 17 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30<sup>th</sup> day of treatment.

19. The method of claim 17 wherein the sustained release formulation is an aqueous nanoparticle suspension.

20. A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment comprising

- (a) administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 50 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

21. The method of claim 20 wherein the sustained release formulation is an aqueous nanoparticle suspension.

22. The method of claim 20 wherein the psychiatric patient is in need of treatment for psychosis.

23. The method of claim 4 wherein the psychiatric patient is in need of treatment for schizophrenia.

24. The method of claim 4 wherein the psychiatric patient is in need of treatment for bipolar disorder.

25. The method of claim 4 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or

EXPERTS\_MYL\_002414  
PTX-115

PTX-0115\_0022

US 2009/0163519 A1

Jun. 25, 2009

19

Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somato-

form Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar TI Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

26. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

- (a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;
- (b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6<sup>th</sup> to about 10th day of treatment; and
- (c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 34th to about the 38th day of treatment.

27. The method of claim 26 wherein the maintenance dose of a sustained release formulation of paliperidone palmitate is administered monthly in the deltoid or gluteal muscle of the psychiatric patient in need after the 30<sup>th</sup> day of treatment.

28. The method of claim 26 wherein the sustained release formulation is an aqueous nanoparticle suspension.

29. A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment comprising

- (a) administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment;

EXPERTS\_MYL\_002415  
PTX-115

PTX-0115\_0023



US 2009/0163519 A1

20

Jun. 25, 2009

(b) administering intramuscularly in the deltoid muscle of the patient in need of treatment a maintenance dose of from about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the eighth day of treatment; and

(c) administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a maintenance dose of about 25 mg-eq. to about 100 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation on about the 36th day of treatment.

30. The method of claim 29 wherein the sustained release formulation is an aqueous nanoparticle suspension.

31. The method of claim 29 wherein the psychiatric patient is in need of treatment for psychosis.

32. The method of claim 29 wherein the psychiatric patient is in need of treatment for schizophrenia.

33. The method of claim 29 wherein the psychiatric patient is in need of treatment for bipolar disorder.

34. The method of claim 29 wherein the psychiatric patient is in need of treatment for a mental disorder selected from the group consisting of Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusional (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder

with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed,

EXPERTS\_MYL\_002416  
PTX-115

PTX-0115\_0024

US 2009/0163519 A1

Jun. 25, 2009

21

Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar

II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.7), and Personality Disorders, Borderline (301.83).

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**Appx10489**



**PTX-0115\_0026**

**Appx10490**

**PTX-0116**

US 20110105536A1

(19) **United States**(12) **Patent Application Publication**  
**Lewyn-Briscoe et al.**(10) **Pub. No.: US 2011/0105536 A1**(43) **Pub. Date: May 5, 2011**(54) **DOSING REGIMEN ASSOCIATED WITH  
LONG-ACTING INJECTABLE  
PALIPERIDONE ESTERS****Publication Classification**(51) **Int. Cl.***A61K 31/519*

(2006.01)

*A61P 25/18*

(2006.01)

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NJ (US); **David W. Hough**,  
Wallingford, PA (US); **Bart M.M.**  
**Remmerle**, Gent (BE); **Mahesh N.**  
**Samtani**, Flemington, NJ (US)(52) **U.S. Cl. .... 514/259.41**

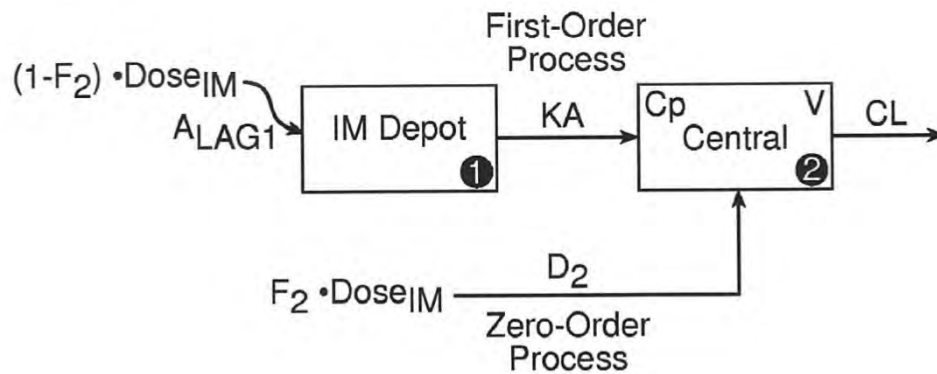
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**ABSTRACT**(21) **Appl. No.: 12/916,910**(22) **Filed: Nov. 1, 2010****Related U.S. Application Data**(60) **Provisional application No. 61/256,696, filed on Oct.  
30, 2009.**

The present application provides a method for treating patients in need of psychiatric treatment, wherein said patient misses a stabilized dose of a monthly maintenance regimen of paliperidone palmitate. The present application also provides a method for treating psychiatric patients in need of a switching treatment to paliperidone palmitate in a sustained release formulation.

MYL-PP3M056044

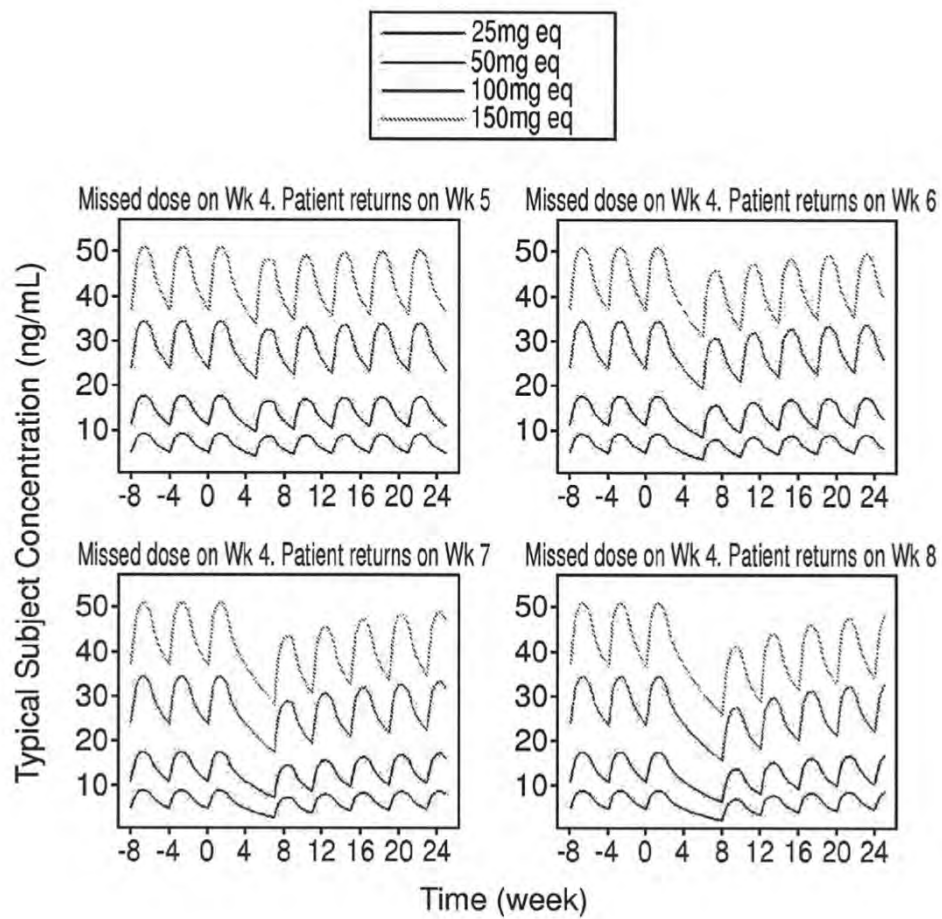
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**FIG. 1**

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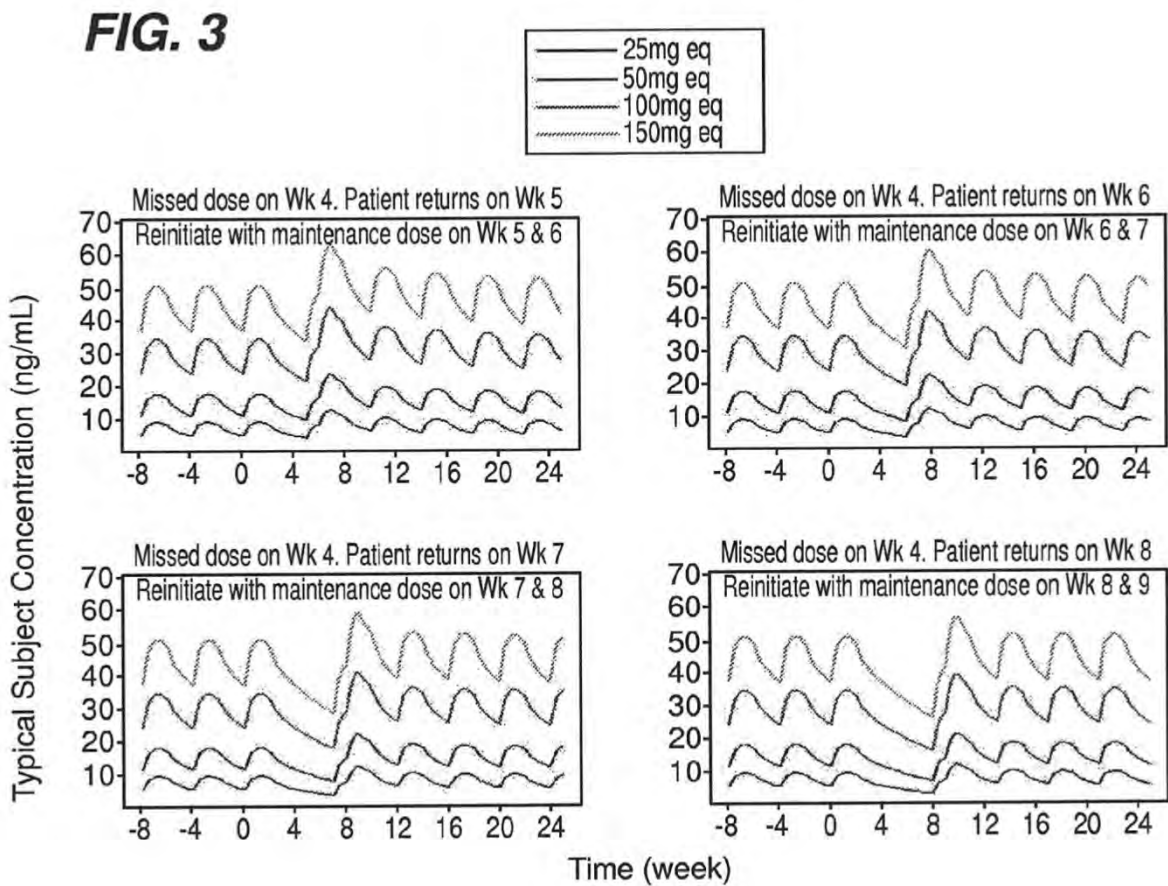
**FIG. 2**



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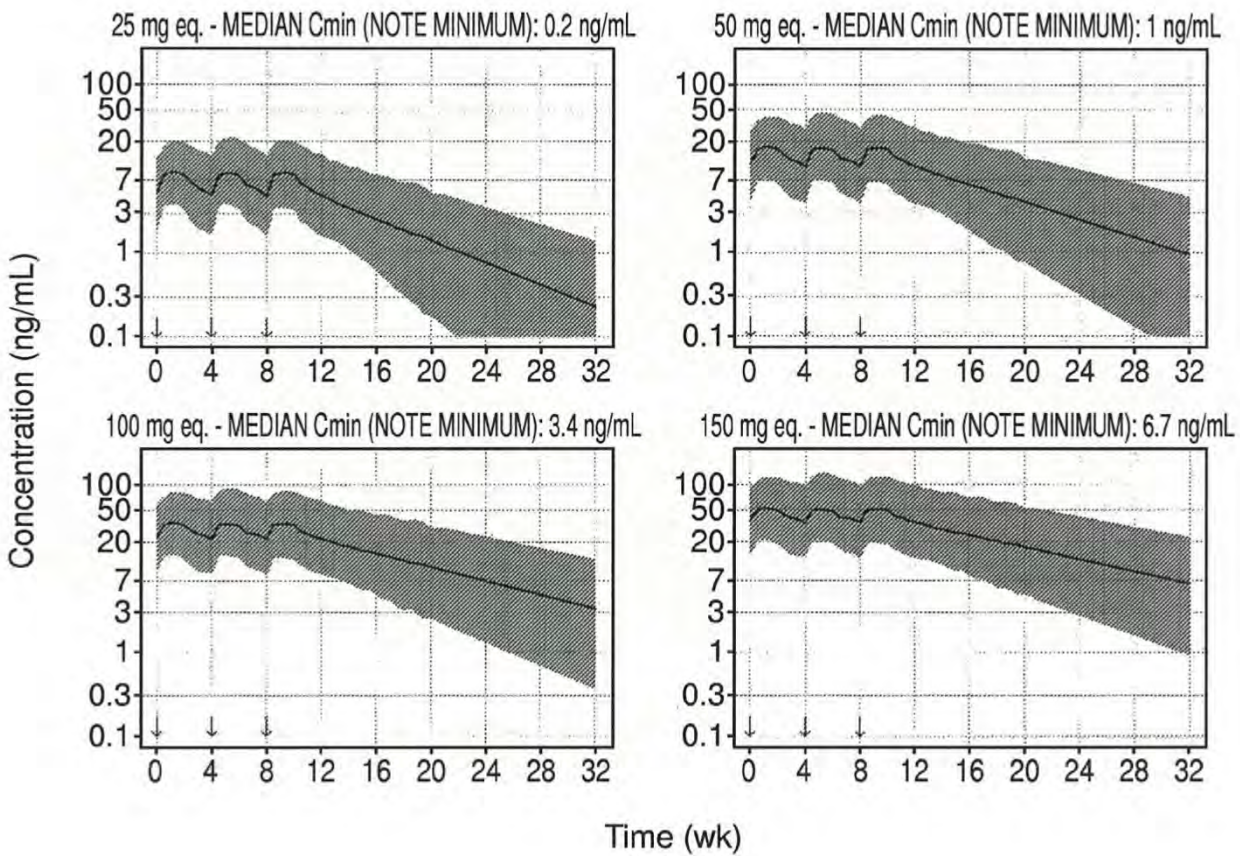
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Appx10494

**FIG. 4**



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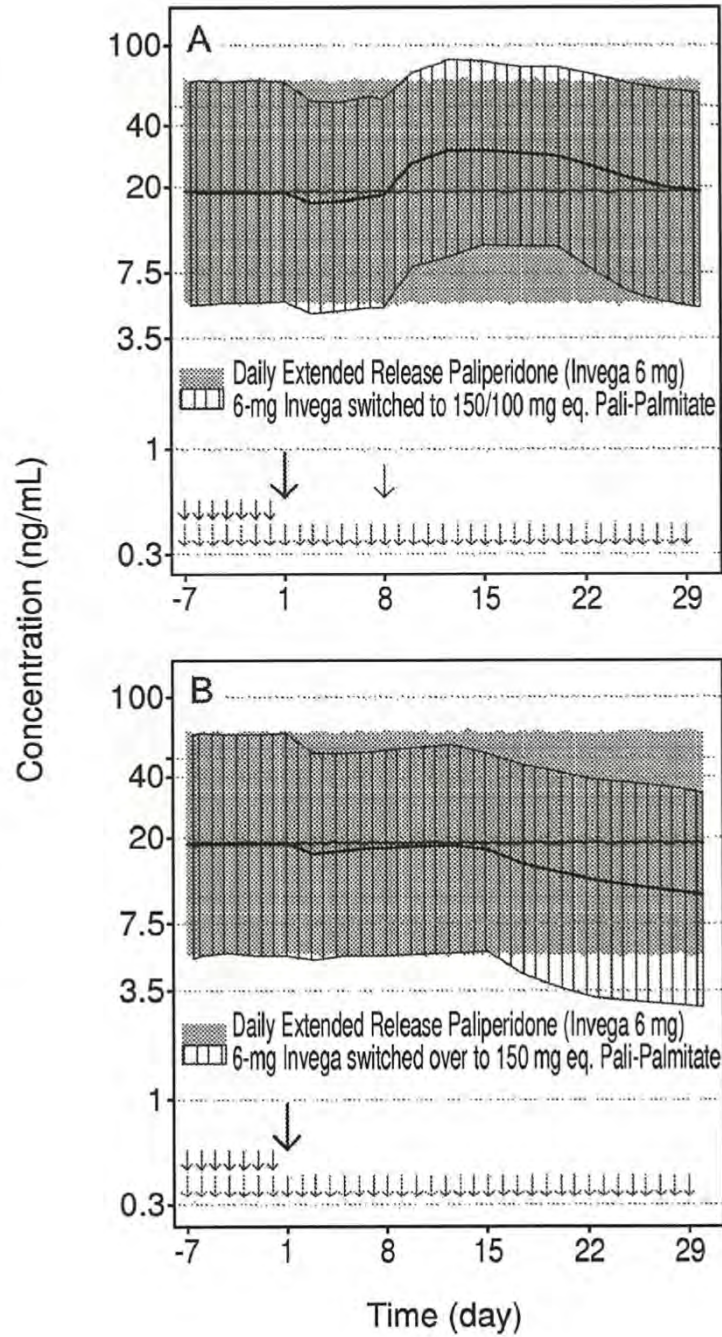
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**FIG. 5**

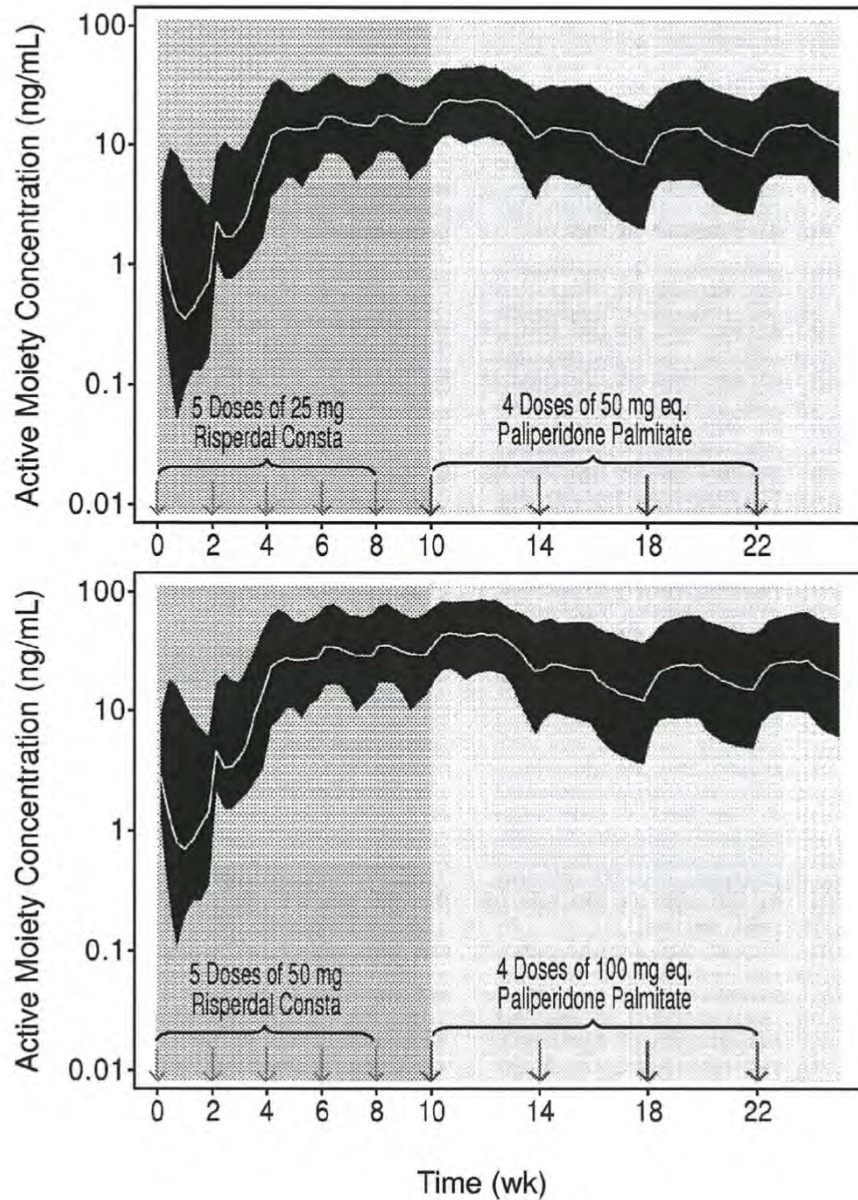


MYL-PP3M056049

**PTX-116**

**PTX-0116\_0006**

**FIG. 6**



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**PTX-116**

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US 2011/0105536 A1

May 5, 2011

1

## DOSING REGIMEN ASSOCIATED WITH LONG-ACTING INJECTABLE PALIPERIDONE ESTERS

### CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application 61/256,696, filed on Oct. 30, 2009, which is incorporated by reference herein in its entirety.

### FIELD OF THE INVENTION

[0002] This invention relates to a method for treating patients in need of switching treatment from other antipsychotic drug to long-acting injectable paliperidone palmitate formulations.

### BACKGROUND OF THE INVENTION

[0003] Antipsychotic medications are the mainstay in the treatment of schizophrenia, schizoaffective disorder, and schizophreniform disorders. Conventional antipsychotics were introduced in the mid-1950s. These typical or first generation drugs are usually effective in controlling the positive symptoms of schizophrenia, but are less effective in moderating the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, typified by risperidone and olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia.

[0004] Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D<sub>2</sub> and serotonin (5-hydroxytryptamine type 2A) antagonism of the second generation, atypical antipsychotic drugs. Paliperidone is the major active metabolite of risperidone. Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) for the treatment of schizophrenia and maintenance of effect.

[0005] Paliperidone palmitate is being developed as a long-acting, intramuscular (i.m.), injectable aqueous nanosuspension for the treatment of schizophrenia and other related diseases that are normally treated with antipsychotic medications. Because of extreme low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an i.m. injection before being hydrolyzed to paliperidone and made available in the systemic circulation.

[0006] Many patients with the mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. compliance problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies. Paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly, which may greatly enhance compliance with dosing. Paliperidone palmitate formulated as an aqueous nanosuspension is described in U.S. Pat. Nos. 6,577,545 and 6,555,544. In addition, a dosing regimen of paliperidone palmitate for treating patients is disclosed in US Patent Application Publication No. 20090163519.

[0007] Paliperidone palmitate is an atypical antipsychotic drug administered by injection. Paliperidone palmitate may be administered at flexible injection sites including gluteal or deltoid muscle. Previous oil-based antipsychotic agents are indicated for gluteal muscle injection and may be associated with pain on injection, which may cause undesired effects of needle phobia and perceived injection pain. This may reduce patients' acceptance towards these medications and result in a negative influence on the clinical management of these patients. The administration of paliperidone palmitate at flexible injection sites may improve patients' acceptance and compliance to psychotic treatment.

[0008] In addition, paliperidone palmitate provides benefits of sustained dose release in plasma without significant concentration variation, regular monitor, reduced side effects and increased treatment efficacy. The administration of paliperidone palmitate may improve effectiveness of psychotic treatment.

[0009] Therefore, there may be an increasing demand to switch treatment of patients in need thereof from oral or injectable antipsychotic drugs to paliperidone palmitate. Further, there is a need to reinstitute a dosing regimen for patients who misses their maintenance or stabilized dose. Thus, the objective of the present application is to provide a dosing regimen of paliperidone palmitate for patients in need of a treatment switching from other antipsychotic agents to paliperidone palmitate. Another objective of the present application is to provide a dosing regimen of paliperidone palmitate for patients who have missed the monthly maintenance or stabilized dosing regimen of paliperidone palmitate.

### SUMMARY OF THE INVENTION

[0010] In one embodiment of the present application a dosing regimen is provided for administering paliperidone palmitate to a patient in need of psychiatric treatment, wherein said patient misses a stabilized monthly maintenance dose for more than about 4 weeks and less than about 6 weeks, comprising administering intramuscularly in the deltoid a first reinitiation loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; and administering intramuscularly in the gluteal a reinitiation maintenance dose of paliperidone as a paliperidone ester in a sustained release formulation on the 23<sup>rd</sup> day to about the 37<sup>th</sup> day or between about 30±7 day after said first day of treatment.

[0011] In another embodiment of the present application a dosing regimen is provided for administering paliperidone esters to a patient in need of psychiatric treatment, wherein said patient misses a stabilized monthly maintenance dose for more than about 6 weeks, comprising administering intramuscularly in the deltoid a first reinitiation loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid a second reinitiation loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation 1 week later (on the eighth day of treatment); and administering intramuscularly in the gluteal a reinitiation maintenance dose of paliperidone as a paliperidone ester in a sustained release formulation on about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day or between about 30±7 days after said first day of treatment.

[0012] According to the present application, the first reinitiation dose and the second reinitiation dose may be the same dosing as the stabilized monthly maintenance dose. Further,

MYL-PP3M056051

PTX-116

PTX-0116\_0008

US 2011/0105536 A1

May 5, 2011

2

the first reinitiation dose, the second reinitiation dose and the reinitiation maintenance dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation may range from about 39 mg to about 234 mg.

[0013] In yet another embodiment of the present application a dosing regimen is provided for administering paliperidone palmitate to a psychiatric patient in need of a switching treatment to paliperidone palmitate, wherein said patient has received injectable antipsychotic drugs other than paliperidone palmitate, comprising administering intramuscularly in the deltoid of said patient a first loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; and administering intramuscularly in the deltoid or gluteal muscle of said patient a maintenance dose of paliperidone palmitate in a sustained release formulation on about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day or between about 30±7 days after said first day of treatment.

[0014] In a further embodiment of the present application a dosing regimen is provided for administering paliperidone palmitate to a psychiatric patient in need of a switching treatment to paliperidone palmitate, wherein said patient has received injectable antipsychotic drugs other than paliperidone palmitate, comprising administering intramuscularly in the deltoid of said patient a first loading dose of paliperidone as a paliperidone palmitate formulated in a sustained release formulation on the first day of treatment; administering intramuscularly in the deltoid or gluteal muscle of said patient a maintenance dose of paliperidone palmitate in a sustained release formulation on about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day or between about 30±7 days after said first day of treatment; and administering in the deltoid or gluteal muscle of said patient said maintenance dose of paliperidone palmitate in a sustained release formulation monthly thereafter.

[0015] According to the present application, the first dose and the maintenance dose of paliperidone for the switch treatment as a paliperidone palmitate formulated in a sustained release formulation may range from about 39 mg to about 234 mg.

[0016] Further according to the present application, the first dose and the maintenance dose of paliperidone for the switch treatment as a paliperidone palmitate formulated in a sustained release formulation may range from about 39 mg to about 234 mg.

[0017] This and other objects and advantages of the present invention may be appreciated from a review of the present applications.

#### DETAILED DESCRIPTION OF FIGURES

[0018] FIG. 1. Diagram of the final model for paliperidone palmitate.

[0019] FIG. 2. Simulations for reinitiation treatment of patients who missed the week 4 dose at about weeks 5, 6, 7, and 8 with a single maintenance dose of at day 1.

[0020] FIG. 3. Simulation of reinitiation treatment of patients who missed the week 4 dose at about weeks 5, 6, 7, and 8 with two maintenance doses at day 1/day 8.

[0021] FIG. 4: Plasma concentration profiles of steady-state paliperidone palmitate following more than about 6 months of treatment lapse, using various doses of paliperidone palmitate.

[0022] FIG. 5. Switching treatment from oral paliperidone ER to paliperidone palmitate. Pink shaded areas represent patients stabilized on oral ER paliperidone and continuing oral therapy. (A) Hatched area represents patients switched to

paliperidone palmitate on day 1 using the day1/day8 initiation. (B) Hatched area represents patients switched to paliperidone palmitate on day 1 using a single initiation dose alone. Lines & shaded/hatched areas represent median and about 90% prediction intervals; arrows indicate dosing times.

[0023] FIG. 6. Switching from RISPERDAL® CONSTA® to paliperidone palmitate. Top panel represents the low dose and the bottom panel represents the high dose. Simulations for the middle dose are not shown because those results can be simply interpolated between the 2 panels. Lines and shaded areas (violet region) represent medians and about 90% prediction intervals.

#### DETAILED DESCRIPTION

[0024] In one aspect the present application provides a dosing regimen for paliperidone palmitate comprising administering a initial dosing at the first day of treatment and administering a maintenance dosing on between 30±7 days after the first day of treatment.

[0025] Paliperidone palmitate is a long-acting intramuscular injectable atypical antipsychotic. Paliperidone palmitate is an ester of paliperidone which has been approved in the US and other countries for the acute and maintenance treatment of patients with schizophrenia. Following intramuscular injection, paliperidone is released into the systemic circulation over an extended period of time, allowing for once-monthly dosing without the need for oral supplementation.

[0026] U.S. Patent Application No. 20090163519 has disclosed a dosing regimen for treating a psychiatric patient using paliperidone as a paliperidone palmitate ester in a sustained release formulation. To attain a therapeutic plasma level of paliperidone, patients are administered to receive a first dose of paliperidone palmitate on day 1 of treatment, followed by a second dose between days 6 to 10 of treatment, then a third dose between days 34 to 38 of treatment. It is preferred that the patients will be administered the first dose on day 1, the second dose on day 8 after the first dose and the third dose on day 36 of after the first dose. The first two doses may be injected in the deltoid muscle. Thereafter paliperidone palmitate may be administered by injection approximately once a month (e.g. once every four weeks). To assure a potential therapeutic plasma level of paliperidone is attained, at least the first loading dose of about 150 mg-eq. of paliperidone as a paliperidone palmitate ester may be administered on day 1 of treatment. To further assure a potential therapeutic plasma level of paliperidone is attained by the patient, the first loading dose and the second loading dose ranging between from about 100 mg-eq. to about 150 mg-eq. of paliperidone as a paliperidone palmitate ester may be administered. To maintain a therapeutic level in the plasma, the subsequent doses thereafter or the maintenance dose ranging from about 25 mg-eq. to 150 mg-eq. per month may be administered. The maintenance dose may be administered intramuscularly into the deltoid or gluteal muscle, and the gluteal muscle is preferred. Those of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patients' conditions such as response to the medication and renal function.

[0027] Due to the improved drug efficacy, long-acting sustained release formulation, and reduced side effects of paliperidone palmitate, there may be clinical need and increasing demand to switch patients from previous antipsychotic drugs to paliperidone palmitate.

MYL-PP3M056052

PTX-116

PTX-0116\_0009



US 2011/0105536 A1

May 5, 2011

3

[0028] As described herein, various dosing regimen including switching treatment and reinitiation treatment for paliperidone palmitate is generated from comprehensive pharmacokinetic models or simulations based on clinical data. The models or simulations provide useful, efficient and cost-effective treatment since there is no systematically collected clinical data to specifically address switching schizophrenia patients from other antipsychotics to paliperidone palmitate or concerning concomitant administration with other antipsychotics. Based on the extensive analysis of Phases I, II and III clinical trials with schizophrenia patients, the pharmacokinetic models provide an optimal effective regimen for switching treatment of patients from other antipsychotic drug to paliperidone palmitate and reinitiation treatment of patients missed their stabilized doses of paliperidone palmitate.

[0029] The models have indicated that there may be flexibility in the duration of the second loading dose and the maintenance dose of the maintenance dosing regimen. For example, the second loading dose may be administered within the duration of about the 8<sup>th</sup> day $\pm$ 2 days (or about 1 week $\pm$ 2 days) after administering of the first loading dose. Therefore, the second loading dose may be administered from about the 6<sup>th</sup> to about the 10<sup>th</sup> day after the first loading dose of the initial dosing. Similarly, the maintenance dose may be administered within the duration of about the 30<sup>th</sup> day $\pm$ 7 days after administering of the first loading dose. Therefore, the maintenance dose may be administered from about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day after administering of the first loading dose of the initial dosing. The flexible administration timing provides additional treatment benefit for patients who may require earlier administration or have missed their dose, within a short window, of the scheduled treatment without affecting the treatment effectiveness.

[0030] The models or simulations also indicate that paliperidone palmitate may be administered by intramuscular injection into either deltoid or gluteal muscle. The first and second loading dose of the initiation regimen may be administered in the deltoid muscle and the maintenance dose of the maintenance regimen may be administered in either the deltoid or gluteal muscle. The injection into the deltoid muscle may be delivered by a 1-inch 23-Gauge (G) or 1.5-inch 22-G needle based on the patient's weight. For the patients whose body weights are less than about 90 kg or 200 lb, a 1-inch 23-G needle may be used for administration, and for those body weights are equal or more than about 90 kg or 200 lb, a 1.5-inch 22-G needle may be used for administration. The injection into the gluteal muscle may be delivered by a 1.5-inch 22-G needle for all body weights.

[0031] One aspect of the present application provides a method or dosing regimen for treating patients switching from previous injectable or oral antipsychotic drug to paliperidone palmitate. The previous injectable antipsychotic drug may include but not limited to clopenthixol decanoate, perphenazine enanthate, pipothiazine palmitate, haloperidol decanoate, fluspirilene, zuclopenthixol decanoate, flupenthixol decanoate, fluphenazine decanoate, fluphenazine enanthate, risperidone microspheres, olanzapine pamoate and the like. The previous oral antipsychotic drug may include oral typical antipsychotic such as chlorpromazine, flupenthixol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thioridazine, thiothixene, trifluoperazine or the like; and oral atypical antipsychotic drug such as amisulpride, aripiprazole,

clozapine, olanzapine, quetiapine, risperidone active moiety, sertindole, ziprasidone and the like.

[0032] For patients who have previously received injectable antipsychotic drugs, a switching treatment to paliperidone palmitate may comprise an initiation dosing regimen and a maintenance dosing regimen. The switching treatment may be initiated in place of the next scheduled injection. It is found herein that one dosing of paliperidone palmitate may be sufficient to attain the desired drug levels or plasma concentration of paliperidone during the initial dosing regimen. Accordingly, the initiation dosing regimen for switching patients from other injectable antipsychotic may comprise administering a first loading dose of paliperidone palmitate. Thereafter, the patients may be administered with the maintenance dosing regimen of paliperidone palmitate at a monthly schedule. The maintenance dosing regimen may comprise administering a maintenance dose of paliperidone palmitate on between days 23 to 37 after the first loading dose.

[0033] The dose of the switching treatment from previous injectable antipsychotic may be determined based on the condition of the patient and/or the severity of the disease. The preferred first loading dose may range from about 156 mg to about 234 mg of paliperidone palmitate, and more preferably about 234 mg. The preferred monthly maintenance dose may range from about 39 to about 234 mg, and more preferably about 117 mg. Based on the patient tolerability and/or the drug efficacy, the maintenance dose may be further adjusted monthly to achieve optimal treatment effectiveness.

[0034] By way of example, a dosing regimen is provided to switch patients from other injectable antipsychotic drug to paliperidone palmitate comprising administering into the deltoid muscle the initial dosing regimen comprising a first loading dose of about 234 mg of paliperidone palmitate and administering into the deltoid or gluteal muscle the maintenance regimen comprising a monthly maintenance dose of about 39 to about 234 mg of paliperidone palmitate on about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day after administering of the first loading dose.

[0035] For patients who have previously received oral antipsychotic drugs, a switching treatment to paliperidone palmitate may comprise an initial dosing regimen and a monthly dosing regimen. The initial dosing regimen may comprise administering a first loading dose of paliperidone palmitate and administering a second loading dose of paliperidone palmitate, and the maintenance dosing regimen may comprise administering a maintenance dose of paliperidone palmitate. The previous oral antipsychotics may be discontinued at the time of initiation of the switching treatment or administration of the first loading dosing of paliperidone palmitate.

[0036] To initiate switching treatment from oral antipsychotic drug, paliperidone palmitate may be initiated with the first loading dose on treatment day 1 and the second loading dose one week later, and maintained with the maintenance dose at a monthly schedule. The dose may be determined based on the condition of the patient and/or the severity of the disease. The preferred first loading dose may range from about 156 mg to about 234 mg of paliperidone palmitate, and more preferably about 234 mg. The preferred second loading dose may range from about 78 mg to about 156 mg, and more preferably about 156 mg. The preferred monthly maintenance dose may range from about 39 to about 234 mg, and more preferably about 117 mg. Subsequently, based on the patient

MYL-PP3M056053

PTX-116

PTX-0116\_0010

US 2011/0105536 A1

May 5, 2011

4

tolerability and/or the drug efficacy, the maintenance dose may be further adjusted monthly to achieve optimal treatment effectiveness. The patients may be monitored for several months to ensure the full effect of the dose adjustment because of the prolonged-release characteristic of paliperidone palmitate.

[0037] Based on the pharmacokinetic simulations, patients previously stabilized on paliperidone in oral tablets may attain similar paliperidone steady-state exposure during maintenance treatment with paliperidone palmitate intramuscular injection monthly. For example, patients stabilized on oral paliperidone of about 3 mg may attain similar paliperidone steady-state exposure with the intramuscular injection of paliperidone palmitate of about 39 mg to about 78 mg. Similarly, patients stabilized on oral paliperidone of about 6 mg and about 9 mg may attain similar paliperidone steady-state exposure with the intramuscular injection of paliperidone palmitate of about 117 mg and about 234 mg, respectively. Therefore, during the maintenance regimen, the patients previously stabilized on paliperidone in oral tablets may be administered with the appropriate dose of paliperidone palmitate in injectable formulation corresponding to the stabilized dose of oral paliperidone.

[0038] Another aspect of the present application provides a method for treating patients who have missed the stabilized dosing regimen. As generally recommended in the medical field, a missed dose during treatment regimen should be avoided. Because of the flexibility in the duration of the initiation dosing regimen and the maintenance dosing regimen as discussed above, the second loading dose of the initial regimen may be administered at about the 8<sup>th</sup> day $\pm$ 2 days (1 week $\pm$ 2 days) after administering of the first loading dose. Similarly, the maintenance dose of the maintenance regimen may be administered at about the 30<sup>th</sup> day $\pm$ 7 days after administering of the first loading dose. This may avoid or reduce the frequency of a missed dose of paliperidone palmitate during the treatment.

[0039] Using the pharmacokinetic model or simulation, a dosing regimen is provided for the reinitiation regimen for administering paliperidone palmitate to patients who have missed the monthly maintenance dose by more than about 4 weeks. The reinitiation regimen may depend upon the duration of time lapsed since the last injection of paliperidone palmitate. By way of example, a reinitiation regimen may be provided for treating patients who have missed a dose for more than about 4 weeks and less than about 6 weeks, for more than about 6 weeks and less than about 6 months, and for more than about 6 months.

[0040] When more than about 4 weeks and less than about 6 weeks have elapsed since a patient received the last dosing of paliperidone palmitate, the reinitiation regimen may comprise a first loading dose and a maintenance dose. The first dose of may be administered as soon as possible and the maintenance dose may be administered at monthly intervals after the first loading dose. The duration of the maintenance dose may be flexible, e.g. the maintenance dose may be administered 30 days $\pm$ 7 days or the 23<sup>rd</sup> day to the 37<sup>th</sup> day after the first loading dose. It is found herein that the administration of a single dose of paliperidone palmitate at the treatment day 1 provides sufficient drug levels or plasma concentrations of paliperidone. Therefore, a second loading dose at day 8 is not needed for treating the patients who missed stabilized dose for less than about 6 weeks.

[0041] The first dose and the maintenance dose may be the same dosing amount as the previously stabilized dose of the maintenance regimen prior to the missed dose. Each of the first and the maintenance doses of the reinitiation regimen for less than about 6 weeks may range from about 39 mg to about 234 mg of paliperidone palmitate. Additionally, the maintenance dosing of the reinitiation regimen for less than about 6 weeks may be injected in either deltoid or gluteal muscle.

[0042] In one embodiment, a method of reinitiation regimen is provided for treating patients who have missed a dose for more than about 4 weeks and less than about 6 weeks, comprising administering into the deltoid muscle a first loading dose and administering into the deltoid or gluteal muscle a maintenance dose on about the 23<sup>rd</sup> to about the 37<sup>th</sup> day after the first loading dose. Thereafter, the maintenance may be administered into the deltoid or gluteal muscle at a monthly schedule.

[0043] When more than 6 weeks and less than about 6 months have elapsed since a patient received the last dosing of paliperidone palmitate, the reinitiation regimen may comprise a first loading dose, a second loading dose, and a maintenance dose. The first dose of may be administered as soon as possible, the second dose may be administered at about the 8<sup>th</sup> days (or about 1 week) after the first loading dose, and a maintenance dosing may be administered at about the 30<sup>th</sup> day after the first loading dose. Thereafter, the maintenance dose may be administered at monthly intervals. The duration of the second loading dose and the maintenance dose may be flexible. For example, the second loading dose may be administered 8 days $\pm$ 2 days or the 6<sup>th</sup> day to the 10<sup>th</sup> day after the first loading dose and the maintenance dose may be administered 30 days $\pm$ 7 days (or the 23<sup>rd</sup> day to the 37<sup>th</sup> day) after the first loading dose. The first dose and the second dose of the reinitiation regimen for more than about 6 weeks and less than 6 months may be injected in deltoid muscle to provide a quick attainment to the desired drug levels or plasma concentrations of paliperidone. The first dose and the second dose may depend on the stabilized dose prior to the missed dose. By way of example, when the stabilized dose prior to the missed dose is less than about 234 mg of paliperidone palmitate, the first loading dose and the second loading dose may be the same dosing amount as the stabilized dose prior to the missed dose. For example, each of the first loading dose and the second loading dose may range from about 39 mg to about 156 mg of paliperidone palmitate. By way of another example, when the stabilized dose prior to the missed dose is about 234 mg of paliperidone palmitate, the first loading dose may be administered at about 156 mg and the second loading dose may be administered at about 156 mg. Thereafter, the maintenance dosing may range from about 39 mg to about 234 mg of paliperidone palmitate and may be injected in either deltoid or gluteal muscle.

[0044] In another embodiment, a method of reinitiation regimen is provided for treating patients who have missed a dose for more than about 6 weeks and less than 6 months, comprising administering into the deltoid muscle a first loading dose, administering into the deltoid muscle a second loading dose on about the 6<sup>th</sup> day to the 10<sup>th</sup> day after the first loading dose, and administering into the deltoid or gluteal muscle a maintenance dose on about the 23<sup>rd</sup> day to the 37<sup>th</sup> day after the first loading dose. Thereafter, the maintenance dose may be administered at monthly intervals.

[0045] When more than about 6 months have elapsed since a patient received the last dosing of paliperidone palmitate,

MYL-PP3M056054

PTX-116

PTX-0116\_0011



US 2011/0105536 A1

May 5, 2011

5

the reinitiation regimen may comprise a first loading dose, a second loading dose and a maintenance dose. The first dose may be administered as soon as possible, the second dose may be administered on about the 8<sup>th</sup> day after the first loading dose, and a maintenance dosing may be administered on about 30<sup>th</sup> day after the first loading dose. The duration of the second loading dose and the maintenance dose of the reinitiation regimen may be flexible. For example, the second loading dose may be administered 7th day $\pm$ 2 days or the 6<sup>th</sup> day to the 10<sup>th</sup> day after the first loading dose and the maintenance dose may be administered about 30 day $\pm$ 7 days or the 23<sup>rd</sup> day to the 37<sup>th</sup> day after the loading dose.

[0046] The dose of the reinitiation regimen for more than about 6 months may be determined based on the condition of the patient and/or the severity of the disease. The preferred first loading dose may range from about 156 mg to about 234 mg of paliperidone palmitate, and more preferably about 234 mg. The preferred second loading dose may range from about 78 mg to about 156 mg, and more preferably about 156 mg. The preferred monthly maintenance dose may range from about 39 to about 234 mg, and more preferably about 117 mg. Subsequently, based on the patient tolerability and/or the drug efficacy, the maintenance dose may be further adjusted monthly to achieve optimal treatment effectiveness. The patients may be monitored for several months to ensure the full effect of the dose adjustment because of the prolonged-release characteristic of paliperidone palmitate. Further, the first dose and the second dose of the reinitiation regimen for patients who have missed the dose for more than about 6 months may be injected in deltoid muscle. The maintenance dose of the reinitiation regimen for patients who have missed the dose for more than about 6 weeks may be injected in either deltoid or gluteal muscle.

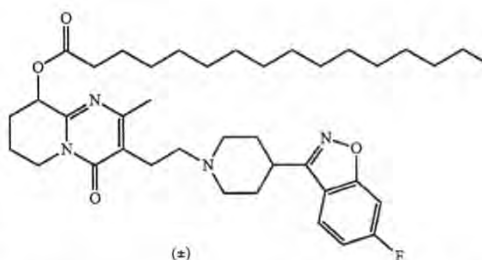
[0047] In yet another embodiment, a method of reinitiation regimen is provided for treating patients who have missed a dose for more than about 6 months, comprising administering into the deltoid muscle a first loading dose, administering into the deltoid muscle a second loading dose on about the 6<sup>th</sup> to about the 10<sup>th</sup> day and administering into the deltoid or gluteal muscle a maintenance dose on about the 23<sup>rd</sup> day to about the 37<sup>th</sup> day after administering of the first loading dose. Thereafter, the maintenance dose may be administered at monthly intervals.

[0048] As used herein, the term "stabilized dose" refers to the dose which is to be administered according to the established dosing regimen. Preferably, the stabilized dose may be the maintenance dose of the monthly maintenance dosing regimen prior to a missed dose.

[0049] Also used herein, the terms "the first loading dose of the reinitiation regimen", "the first dose of the reinitiation regimen", "the first reinitiation dose" or variant thereof refer to the dose to be administered on day 1 when patients return to treatment. Similarly, the terms "the second loading dose of the reinitiation regimen", "the second dose of the reinitiation regimen", "the second reinitiation dose" or variant thereof refer to the dose to be administered after a week after the treatment day 1; and the terms "the maintenance dose of the reinitiation regimen", "the reinitiation maintenance dose" or variant thereof refer to the dose to be administered monthly after the treatment day 1.

[0050] Paliperidone esters are psychotic agents belonging to the chemical class of benzisoxazole derivatives, which contains a racemic mixture of (+)- and (-)-paliperidone, which are described in U.S. Pat. No. 5,254,556 (incorporated

herein by reference). The chemical name for paliperidone palmitate is (+)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyrido[1,2-c]pyrimidin-9-yl hexadecanoate. The structural formula is:



[0051] Paliperidone esters may be formulated with pharmaceutical excipients into injectable dosage forms as described in U.S. Pat. Nos. 5,254,556 and 6,077,843 both of which are incorporated herein by reference. Injectable formulations may be formulated in aqueous carriers.

[0052] Suitable aqueous depot formulations are described in U.S. Pat. No. 6,077,843 which is incorporated herein by reference. The aqueous formulation would preferably be a nano particle suspension of wherein the nano particles would be of an average size of less than about 2,000 nm to about 100 nm. Preferably the nano particles would have an average particle size (d50) of from about 1,600 nm to about 400 nm and most preferably about 1,400 nm to about 900 nm. Preferably the d90 will be less than about 5,000 nm and more preferably less than about 4,400 nm. As used herein, an effective average particle size (d50) of less than about 2,000 nm means that at least 50% of the particles have a diameter of less than about 2,000 nm when measured by art-known conventional techniques, such as sedimentation field flow fractionation, photon correlation spectroscopy or disk centrifugation. With reference to the effective average particle size, it is preferred that at least about 90%, e.g. about 5,000 nm. Most preferably, about 90% of the particles have a size of less than about 4,400 nm.

[0053] Suitable aqueous nanoparticle depot formulations are described in U.S. Pat. No. 6,555,544 which is incorporated herein by reference. In one embodiment of the present invention the formulation would comprise nanoparticles, a surfactant, a suspending agent, and optionally one or more additional ingredients selected from the group consisting of preservatives, buffers and an isotonicizing agent.

[0054] Useful surface modifiers are believed to include those that physically adhere to the surface of the active agent but do not chemically bond thereto. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants. Representative examples of excipients include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers

MYL-PP3M056055

PTX-116

PTX-0116\_0012

US 2011/0105536 A1

May 5, 2011

6

such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available TWEEN<sup>SM</sup>, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phtalate, noncrystalline cellulose, magnesium aluminate silicate, triethanolamine, polyvinyl alcohol (PVA), poloxamers, tyloxapol and polyvinylpyrrolidone (PVP). Most of these excipients are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986. The surface modifiers are commercially available and/or can be prepared by techniques known in the art. Two or more surface modifiers can be used in combination.

[0055] Particularly preferred surface modifiers include polyvinylpyrrolidone; tyloxapol; poloxamers, such as PLURONIC<sup>SM</sup> F68, F108 and F127 which are block copolymers of ethylene oxide and propylene oxide available from BASF; poloxamines, such as TETRONIC<sup>SM</sup> 908 (T908) which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine available from BASF; dextran; lecithin; Aerosol OT<sup>SM</sup> (AOT) which is a dioctyl ester of sodium sulfosuccinic acid available from Cytec Industries; DUPONOL<sup>SM</sup> P which is a sodium lauryl sulfate available from DuPont; TRITON<sup>SM</sup> X-200 which is an alkyl aryl polyether sulfonate available from Rohm and Haas; TWEEN<sup>SM</sup> 20, 40, 60 and 80 which are polyoxyethylene sorbitan fatty acid esters available from ICI Speciality Chemicals; SPAN<sup>SM</sup> 20, 40, 60 and 80 which are sorbitan esters of fatty acids; ARLACEL<sup>SM</sup> 20, 40, 60 and 80 which are sorbitan esters of fatty acids available from Hercules, Inc.; CARBOWAX<sup>SM</sup> 3550 and 934 which are polyethylene glycols available from Union Carbide; CRODESTA<sup>SM</sup> F110 which is a mixture of sucrose stearate and sucrose distearate available from Croda Inc.; CRODESTA<sup>SM</sup> SL-40 which is available from Croda, Inc.; hexyldecyl trimethyl ammonium chloride (CTAC); bovine serum albumin and SA90HCO which is  $C_{18}H_{37}CH_2(CON(CH_3)CH_2(CHOH)_4CH_2OH)_2$ . The surface modifiers which have been found to be particularly useful include tyloxapol and a poloxamer, preferably, Pluronic<sup>SM</sup> F108 and Pluronic<sup>SM</sup> F68.

[0056] Pluronic<sup>SM</sup> F108 corresponds to poloxamer 338 and is the polyoxyethylene, polyoxypropylene block copolymer that conforms generally to the formula  $HO[CH_2CH_2O]_x[CH(CH_3)CH_2O]_y[CH_2CH_2O]_zH$  in which the average values of x, y and z are respectively 128, 54 and 128. Other commercial names of poloxamer 338 are Hodag NONIONIC<sup>SM</sup> 1108-F available from Hodag, and SYNPERONIC<sup>SM</sup> PE/F108 available from ICI Americas.

[0057] The optimal relative amount of paliperidone palmitate and the surface modifier depends on various parameters. The optimal amount of the surface modifier can depend, for example, upon the particular surface modifier selected, the critical micelle concentration of the surface modifier if it forms micelles, the surface area of the antipsychotic agent, etc. The specific surface modifier preferably is present in an amount of about 0.1 to about 1 mg per square meter surface area of the paliperidone palmitate. It is preferred in the case of paliperidone palmitate (9-hydroxyrisperidone palmitate) to

use PLURONIC<sup>SM</sup> F108 as a surface modifier, a relative amount (w/w) of both ingredients of approximately 6:1 is preferred.

[0058] The particles of this invention can be prepared by a method comprising the steps of dispersing paliperidone palmitate in a liquid dispersion medium and applying mechanical means in the presence of grinding media to reduce the particle size of the antipsychotic agent to an effective average particle size of less than about 2,000 nm. The particles can be reduced in size in the presence of a surface modifier. Alternatively, the particles can be contacted with a surface modifier after attrition.

[0059] A general procedure for preparing the particles of this invention includes (a) obtaining paliperidone palmitate in micronized form; (b) adding the micronized paliperidone palmitate to a liquid medium to form a premix; and (c) subjecting the premix to mechanical means in the presence of a grinding medium to reduce the effective average particle size.

[0060] The paliperidone palmitate in micronized form may be prepared using techniques known in the art. It is preferred that the particle size of the micronized paliperidone palmitate be less than about 100  $\mu m$  as determined by sieve analysis. If the particle size of the micronized paliperidone palmitate is greater than about 100  $\mu m$ , then it is preferred that the particles of paliperidone palmitate be reduced in size to less than 100  $\mu m$ .

[0061] The micronized paliperidone palmitate can then be added to a liquid medium in which it is essentially insoluble to form a premix. The concentration of paliperidone palmitate in the liquid medium (weight by weight percentage) can vary widely and depends on the selected antipsychotic agent, the selected surface modifier and other factors. Suitable concentrations of paliperidone palmitate in compositions vary from about 0.1% to about 60%, preferably is from about 0.5% to about 30%, and more preferably, is approximately 7% (w/v). It is currently preferred to use a concentration of about 100 mg eq of paliperidone per ml or about 156 mg of paliperidone palmitate per ml.

[0062] A more preferred procedure involves the addition of a surface modifier to the premix prior to its subjecting to mechanical means to reduce the effective average particle size. The concentration of the surface modifier (weight by weight percentage) can vary from about 0.1% to about 90%, preferably from about 0.5% to about 80%, and more preferably is approximately 7% (w/v).

[0063] The premix can be used directly by subjecting it to mechanical means to reduce the effective average particle size in the dispersion to less than about 2,000 nm. It is preferred that the premix be used directly when a ball mill is used for attrition. Alternatively, the antipsychotic agent and, optionally, the surface modifier, can be dispersed in the liquid medium using suitable agitation such as, for example, a roller mill or a Cowles type mixer, until a homogeneous dispersion is achieved.

[0064] The mechanical means applied to reduce the effective average particle size of the antipsychotic conveniently can take the form of a dispersion mill. Suitable dispersion mills include a ball mill, an attritor mill, a vibratory mill, a planetary mill, media mills—such as a sand mill and a bead mill. A media mill is preferred due to the relatively shorter milling time required to provide the desired reduction in particle size. For media milling, the apparent viscosity of the premix preferably is anywhere between about 0.1 Pa-s and

MYL-PP3M056056

PTX-116

PTX-0116\_0013



US 2011/0105536 A1

May 5, 2011

7

about 1 Pa·s. For ball milling, the apparent viscosity of the premix preferably is anywhere between about 1 mPa·s and about 100 mPa·s.

[0065] The grinding media for the particle size reduction step can be selected from rigid media preferably spherical or particulate in form having an average size less than about 3 mm and, more preferably, less than about 1 mm. Such media desirably can provide the particles of the invention with shorter processing times and impart less wear to the milling equipment. The selection of the material for the grinding media is believed not to be critical. However, about 95% ZrO stabilized with magnesia, zirconium silicate, and glass grinding media provide particles which are acceptable for the preparation of pharmaceutical compositions. Further, other media, such as polymeric beads, stainless steel, titania, alumina and about 95% ZrO stabilized with yttrium, are useful. Preferred grinding media have a density greater than about 2.5 g/cm<sup>3</sup> and include about 95% ZrO stabilized with magnesia and polymeric beads.

[0066] The attrition time can vary widely and depends primarily upon the particular mechanical means and processing conditions selected. For rolling mills, processing times of up to two days or longer may be required.

[0067] The particles must be reduced in size at a temperature which does not significantly degrade the antipsychotic agent. Processing temperatures of less than about 30° C. to about 40° C. are ordinarily preferred. If desired, the processing equipment may be cooled with conventional cooling equipment. The method is conveniently carried out under conditions of ambient temperature and at processing pressures which are safe and effective for the milling process.

[0068] The surface modifier, if it was not present in the premix, must be added to the dispersion after attrition in an amount as described for the premix above. Thereafter, the dispersion can be mixed by, for example, shaking vigorously. Optionally, the dispersion can be subjected to a sonication step using, for example, an ultrasonic power supply.

[0069] Aqueous compositions according to the present invention conveniently further comprise a suspending agent and a buffer, and optionally one or more of a preservative and an isotonicizing agent. Particular ingredients may function as two or more of these agents simultaneously, e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonicizing agent.

[0070] Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxypropylene ethers. Preferably sodium carboxymethyl cellulose is used in a concentration of about 0.5 to about 2%, most preferably about 1% (w/v). Suitable wetting agents for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate. Preferably polysorbate 20 is used in a concentration of about 0.5% to about 3%, more preferably about 0.5% to about 2%, most preferably about 1.1% (w/v).

[0071] Suitable buffering agents are salt of weak acids and should be used in amount sufficient to render the dispersion neutral to very slightly basic (up to the pH value of about 8.5), preferably in the pH range of about 7 to about 7.5. Particularly

preferred is the use of a mixture of disodium hydrogen phosphate (anhydrous) (typically about 0.9% (w/v)) and sodium dihydrogen phosphate monohydrate (typically about 0.6% (w/v)). This buffer also renders the dispersion isotonic and, in addition, less prone to flocculation of the ester suspended therein.

[0072] Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic acid, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-gamma-picolinium chloride, phenylmercuric acetate and thimerosal. In particular, it is benzyl alcohol which can be used in a concentration up to about 2% (w/v), preferably up to about 1.5% (w/v).

[0073] Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. The suspensions conveniently comprise from about 0% to about 10% (w/v) isotonicizing agent. Mannitol may be used in a concentration from about 0% to about 7% more preferably, however, from about 1% to about 3% (w/v), especially from about 1.5% to about 2% (w/v) of one or more electrolytes are used to render the suspension isotonic, apparently because ions help to prevent flocculation of the suspended ester. In particular, electrolytes of the buffer serve as isotonicizing agent.

[0074] A particularly desirable feature for an injectable depot formulation relates to the ease with which it can be administered. In particular such an injection should be feasible using a needle as fine as possible in a span of time which is as short as possible. This can be accomplished with the aqueous suspensions of the present invention by keeping the viscosity below about 75 mPa·s, preferably below about 60 mPa·s. Aqueous suspensions of such viscosity or lower can both easily be taken up in a syringe (e.g. from a vial), and injected through a fine needle (e.g. a 21 G 1½ inch, 22 G 2 inch, 22 G 1¼ inch or 23 G 1 inch needle). The preferred needles for injection are 22 G 22 G 1½ inch regular wall and 23 G 1 inch regular wall needles.

[0075] Ideally, aqueous suspensions according to the present invention will comprise as much prodrug as can be tolerated so as to keep the injected volume to a minimum, and as little of the other ingredients as possible. In particular, such a composition will comprise by weight based on the total volume of the composition: (a) from about 3% to 20% (w/v) of the prodrug; (b) from about 0.5% to 2% (w/v) of a wetting agent; (c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5); (d) from about 0.5% to about 2% (w/v) of a suspending agent; (e) up to about 2% (w/v) preservatives; and (f) water q.s. ad 100%. Preferably the aqueous suspension will be made under sterile conditions and no preservatives will be used. Appropriate methods to aseptically prepare paliperidone palmitate are described in WO 2006/114384 which is hereby incorporated by reference herein.

[0076] The preferred aqueous dosage form contains inactive ingredients that are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection. The mg of compound delivered in such a dosage form to the patient may be from about 25 to about 150 mg (e.g. 25 mg, 50 mg, 75 mg, 100 mg, 150 mg) injectable dosage form.

MYL-PP3M056057

PTX-116

PTX-0116\_0014

US 2011/0105536 A1

May 5, 2011

8

[0077] As used herein, a dose or dosing is expressed as milligrams (mg) of paliperidone palmitate. Paliperidone palmitate dosing may also be expressed as mg equivalents (mg eq.) of paliperidone with about 39, 78, 117, 156, and 234 mg of paliperidone palmitate being equivalent to about 25, 50, 75, 100 and 150 mg eq., of paliperidone, respectively.

[0078] The term "antipsychotics" or "antipsychotic drug medication" as used herein means any medication used to decrease or ameliorate the symptoms of psychosis in a person with a psychotic disorder and includes, but is not limited to the following compounds: Acetophenazine Maleate; Alentemol Hydrobromide; Alpertine; Azaperone; Batelapine Maleate; Benperidol; Benzindopyrine Hydrochloride; Brofoxine; Bromperidol; Bromperidol Decanoate; Butaclamol Hydrochloride; Butaperazine; Butaperazine Maleate; Carphenazine Maleate; Carvotoline Hydrochloride; Chlorpromazine; Chlorpromazine Hydrochloride; Chlorprothixene; Cimperene; Cintramide; Clomacran Phosphate; Clopenthixol; Clopimozide; Clopazan Mesylate; Cloroperone Hydrochloride; Clothiapine; Clothixamide Maleate; Clozapine; Cyclophenazine Hydrochloride; properidol; Etazolate Hydrochloride; Fenimide; Flucindole; Flumezapine; Fluphenazine Decanoate; Fluphenazine Enanthate; Fluphenazine Hydrochloride; Fluspiroperone; Fluspirilene; Flutoline; Gevotoline Hydrochloride; Halopemide; Haloperidol; Haloperidol Decanoate; Iloperidone; Imidoline Hydrochloride; Lenperone; Mazapertine Succinate; Mesoridazine; Mesoridazine Besylate; Metiapine; Milenperone; Milipertine; Molindone Hydrochloride; Naranol Hydrochloride; Neflumozide Hydrochloride; Ocaperidone; Olanzapine; Oxiperomide; Penfluridol; Pentiapine Maleate; Perphenazine; Pimozide; Pinoxepin Hydrochloride; Pipamperone; Piperacetazine; Pipotiazine Palmitate; Piquindone Hydrochloride; Prochlorperazine Edisylate; Prochlorperazine Maleate; Promazine Hydrochloride; Quetiapine; Remoxipride; Remoxipride Hydrochloride; Risperidone; Rimcazole Hydrochloride; Seperidol Hydrochloride; Sertindole; Setoperone; Spiperone; Thioridazine; Thioridazine Hydrochloride; Thiothixene; Thiothixene Hydrochloride; Tioperidone Hydrochloride; Tiospirone Hydrochloride; Trifluoperazine Hydrochloride; Trifluoperidol; Triflupromazine; Triflupromazine Hydrochloride; and Ziprasidone Hydrochloride.

[0079] The term "psychiatric patient" as used herein, refers to a human, who has been the object of treatment, or experiment for a "mental disorder" and "mental illness" refer to those provided in the Diagnostic and Statistical Manual (DSM IV), American Psychological Association (APA). Those of ordinary skill in the art will appreciate that paliperidone esters (e.g. paliperidone palmitate) can be administered to psychiatric patients for all the known uses of risperidone. These mental disorders include, but are not limited to, schizophrenia; bipolar disorder or other disease states in which psychosis, aggressive behavior, anxiety or depression is evidenced. Schizophrenia refers to conditions characterized as schizophrenia, schizoaffective disorder and schizophreniform disorders, in DSM-IV-TR such as category 295.xx. Bipolar Disorder refers to a condition characterized as a Bipolar Disorder, in DSM-IV-TR such as category 296.xx including Bipolar I and Bipolar Disorder II. The DSM-IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. Pathologic psychological conditions, which are psychoses or may be asso-

ciated with psychotic features include, but are not limited to the following disorders that have been characterized in the DSM-IV-TR. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994). The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress. Examples of pathologic psychological conditions which may be treated include, but are not limited to, Mild Mental Retardation (317), Moderate Mental Retardation (318.0), Severe Mental Retardation (318.1), Profound Mental Retardation (318.2), Mental Retardation Severity Unspecified (319), Autistic Disorders (299.00), Rett's Disorder (299.80), Childhood Disintegrative Disorders (299.10), Asperger's Disorder (299.80), Pervasive Developmental Disorder Not Otherwise Specified (299.80), Attention-Deficit/Hyperactivity Disorder Combined Type (314.01), Attention-Deficit/Hyperactivity Disorder Predominately Inattentive Type (314.00), Attention-Deficit/Hyperactivity Disorder Predominately Hyperactive-Impulsive Type (314.01), Attention-Deficit/Hyperactivity Disorder NOS (314.9), Conduct Disorder (Childhood-Onset and Adolescent Type 312.8), Oppositional Defiant Disorder (313.81), Disruptive Behavior Disorder Not Otherwise Specified (312.9), Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Alcohol Intoxication Delirium (291.0), Alcohol Withdrawal Delirium (291.0), Alcohol-Induced Persisting Dementia (291.2), Alcohol-Induced Psychotic Disorder with Delusions (291.5), Alcohol-Induced Psychotic Disorder with Hallucinations (291.3), Amphetamine or Similarly Acting Sympathomimetic Intoxication (292.89), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Delusions (292.11), Amphetamine or Similarly Acting Sympathomimetic Induced Psychotic with Hallucinations (292.12), Cannabis-Induced Psychotic Disorder with Delusions (292.11), Cannabis-Induced Psychotic Disorder with Hallucinations (292.12), Cocaine Intoxication (292.89), Cocaine Intoxication Delirium (292.81), Cocaine-Induced Psychotic Disorder with Delusions (292.11), Cocaine-Induced Psychotic Disorder with Hallucinations (292.12), Hallucinogen Intoxication (292.89), Hallucinogen Intoxication Delirium (292.81), Hallucinogen-Induced Psychotic disorder with Delusions (292.11), Hallucinogen-Induced Psychotic disorder with Delusions (292.12), Hallucinogen-Induced Mood Disorder (292.84), Hallucinogen-Induced Anxiety Disorder (292.89), Hallucinogen-Related Disorder Not Otherwise Specified (292.9), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium (292.81), Inhalant-Induced Persisting Dementia (292.82), Inhalant-Induced Psychotic Disorder with Delusions (292.11), Inhalant-Induced Psychotic with Hallucinations (292.12), Inhalant-Induced Mood Disorder (292.89), Inhalant-Induced Anxiety Disorder (292.89), Inhalant-Related Disorder Not Otherwise Specified (292.9), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Delusions (292.11), Opioid Intoxication Delirium (292.81), Opioid-Induced Psychotic Disorder with Hallucinations (292.12), Opioid-Induced Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication

MYL-PP3M056058

PTX-116

PTX-0116\_0015



US 2011/0105536 A1

May 5, 2011

9

Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Delusions (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Psychotic Disorder with Hallucinations (292.12), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Induced Anxiety Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Related Disorder Not Otherwise Specified (292.9), Sedative, Hypnotic or Anxiolytic Intoxication (292.89), Sedation, Hypnotic or Anxiolytic Intoxication Delirium (292.81), Sedation, Hypnotic or Anxiolytic Withdrawal Delirium (292.81), Sedation, Hypnotic or Anxiolytic Induced Persisting Dementia (292.82), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Delusions (292.11), Sedation, Hypnotic or Anxiolytic-Induced Psychotic Disorder with Hallucinations (292.12), Sedation, Hypnotic or Anxiolytic-Induced Mood Disorder (292.84), Sedation, Hypnotic or Anxiolytic-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Intoxication (292.89), Other (or Unknown) Substance-Induced Delirium (292.81), Other (or Unknown) Substance-Induced Persisting Dementia (292.82), Other (or Unknown) Substance-Induced Psychotic Disorder with Delusions (292.11), Other (or Unknown) Substance-Induced Psychotic Disorder with Hallucinations (292.12), Other (or Unknown) Substance-Induced Mood Disorder (292.84), Other (or Unknown) Substance-Induced Anxiety Disorder (292.89), Other (or Unknown) Substance Disorder Not Otherwise Specified (292.9), Obsessive Compulsive Disorder (300.3), Post-traumatic Stress Disorder (309.81), Generalized Anxiety Disorder (300.02), Anxiety Disorder Not Otherwise Specified (300.00), Body Dysmorphic Disorder (300.7), Hypochondriasis (or Hypochondriacal Neurosis) (300.7), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.81), Somatoform Disorder Not Otherwise Specified (300.81), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.30), Schizophrenia, Paranoid Type, (295.30), Schizophrenia, Disorganized (295.10), Schizophrenia, Catatonic Type, (295.20), Schizophrenia, Undifferentiated Type (295.90), Schizophrenia, Residual Type (295.60), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Delusional Disorder (297.1), Brief Psychotic Disorder (298.8), Shared Psychotic Disorder (297.3), Psychotic Disorder Due to a General Medical Condition with Delusions (293.81), Psychotic Disorder Due to a General Medical Condition with Hallucinations (293.82), Psychotic Disorders Not Otherwise Specified (298.9), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Mixed, Severe, with Psychotic Features (296.64), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder, Manic, Severe, with Psychotic Features (296.44), Bipolar Disorder, Depressed, Severe, without Psychotic Features (296.53), Bipolar Disorder, Depressed, Severe, with Psychotic Features (296.54), Bipolar II Disorder (296.89), Bipolar Disorder Not Otherwise Specified (296.80), Personality Disorders, Paranoid (301.0), Personality Disorders, Schizoid (301.20), Personality Disorders, Schizotypal (301.22), Personality Disorders, Antisocial (301.

7), and Personality Disorders, Borderline (301.83). The numbers in parenthesis refer to the DSM-IV-TR categories.

[0080] The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in human that is being sought by a researcher, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

[0081] Those of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above. By way of example, an effective amount of paliperidone for the treatment of mental disorders would be from about 0.01 mg/kg to about 2 mg/kg body weight. For the present invention it is preferred to dose patients with about 25 mg-eq. to about 150 mg eq. paliperidone or about 39 mg to about 234 mg paliperidone palmitate. The amount of paliperidone palmitate is provided in sufficient amount to provide the equivalent dose of paliperidone after the palmitic acid moiety is removed from the ester (e.g. 156 mg corresponds to paliperidone 100 mg). In one embodiment of present invention wherein paliperidone palmitate is administered by intramuscular injection once per month is preferred.

[0082] When asked, approximately half of patients in a 13-week study stated that they preferred deltoid to gluteal injections, with the most common reasons for this preference being that it was easier, less embarrassing and faster than an injection in the gluteal muscle. Moreover, it may be beneficial for patients who favour only deltoid injections due to paranoia and other psychiatric symptomatology. When dosing frequency, aqueous-based formulation and flexibility of injection site to accommodate patients' preference are considered in combination, paliperidone palmitate may provide the advantages of improved convenience and acceptability compared with previous antipsychotic medications. With the availability of paliperidone palmitate, the clinicians may need to manage patients switching treatment from other antipsychotic drugs to paliperidone palmitate.

[0083] The following non-limiting examples are provided to further illustrate the present invention.

#### Example 1

##### Methodology

##### Population Pharmacokinetics Models

[0084] A comprehensive population pharmacokinetics (PK) model was developed for paliperidone palmitate based on data from previous studies of subjects with schizophrenia. Briefly, a 1-compartment model with first-order elimination best described the PK of paliperidone following intramuscular administration of the paliperidone palmitate ester. As shown in FIG. 1, the absorption component of the model allowed a fraction (F2) of the dose to enter the central compartment relatively quickly via a zero-order process with duration D2. After a certain lag-time, the remaining fraction (1-F2) entered the systemic circulation via a first-order process (KA) that determines the shape of the plasma concentration-time curve following injection. NONMEM® Version V (Icon Development Solutions, Ellicott City, Md.) running with NM-TRAN version III was used to conduct all population PK analyses and simulations in accordance to the NONMEM Users Guides (Icon Development Solutions, Ellicott City, Md.). NONMEM was run using the J&JPRD computational grid using Intel FORTRAN 9.0 compiler for Windows.

MYL-PP3M056059

PTX-116

PTX-0116\_0016

US 2011/0105536 A1

May 5, 2011

10

Generation of data sets for NONMEM simulations and visualization of results were performed using S Plus® 6.0 professional release 2 software (Insightful Corporation, Seattle, Wash.). The model building included pooled data from about 1,795 subjects from six Phase 1 studies and five Phase 2 and 3 studies. A total of 18,530 PK samples with valid concentration time-points were part of the population PK database. The final model from the historical population PK analysis [(Pop PK Report Paliperidone Palmitate)], including all significant subject covariates was used as simulation machinery for assessing various dosing regimens for paliperidone palmitate including missed dose treatment and switching treatment. Additionally, a comprehensive population PK model was developed for the extended release oral formulation of paliperidone or INVEGA. The model was constructed using pooled data from about 1,368 subjects with about 21,183 paliperidone concentrations from all phases of the INVEGA drug development. The PK of paliperidone in plasma was best captured using an open 2-compartment disposition model with linear elimination from the central compartment. The absorption was modeled with a sequential zero-order input into a depot compartment and first-order absorption with a lag-time from the depot to the central compartment. The relatively faster absorption of paliperidone from the oral route allowed identification of the distributive peripheral compartment, which is not discernible in the flip-flopped paliperidone palmitate PK data. The final paliperidone model from this historical analysis, including all significant subject covariates, was used for simulating PK exposure from oral paliperidone at various dose levels.

[0085] The PK profiles for about 5,000 subjects were simulated for subjects receiving injectable paliperidone palmitate (INVEGA® SUSTENNA™) and oral paliperidone (INVEGA®). For each data set, the covariates of interest were obtained by resampling from the subject covariates (resampling unit was the subject) available in the subject PK database for paliperidone palmitate and the joint distribution of subject-specific characteristics was maintained. To evaluate the outcome of the simulations, the population median and about 90% prediction interval of the simulated plasma concentration vs. time profiles were plotted together.

[0086] A compartmental model was also developed for RISPERDAL® CONSTA® which included a one-compartment disposition submodel characterized by clearance and volume of distribution and three parallel absorption pathways: an immediate pathway describing the absorption of non-encapsulated risperidone, and a fast and a slow sustained-release pathway. For the model building, data for the RISPERDAL® CONSTA® originating only from the final 20-kg manufacturing scale used in Phase-III trials and "to be marketed" formulation was used as the source information. A two stage approach had to be adopted for modeling RISPERDAL® CONSTA® PK because the active moiety profile after intramuscular administration of risperidone depot microsphere formulations was extremely complex (immediate release of a small amount of non-encapsulated risperidone followed by two sustained-release processes differing in the rate of release along with variable delay in release initiation). The model was fitted to individual concentration-time profiles of active moiety. However, the mixed-effects version of the model which included interindividual variability in parameters could not be fitted due to numerical problems with the NONMEM software. Thus, at the first stage, individual estimates of active moiety (risperidone+paliperidone) PK

parameters were obtained using clinical studies where intensive blood sampling occurred in about 56 subjects. These estimates were used as part of the second step in a non-parametric approach to perform population simulations. For the simulation data set, the parameters of interest were obtained by resampling the individual estimates (n=5,000 subjects) where the resampling unit was the subject. This method was able to retain the joint distribution of subject-specific parameters. It was also noted that a depiction of inter-subject variability computed using this method would be an underestimate due to the small size that was used in building this model. Therefore, the prediction interval for RISPERDAL® CONSTA® simulations should be interpreted with caution. To evaluate the outcome of the simulations, the population median and about 90% prediction interval of the simulated plasma concentration vs. time profiles were plotted together. Oral supplementation used during the first few weeks of RISPERDAL® CONSTA® therapy is ignored in this modeling to simplify this complex exercise.

[0087] To add credence to the simulation exercise for the initiation regimens, model based projections were compared with the limited and/or sparse observed data from clinical studies.

#### Example 2

##### Missed Doses

[0088] To manage patients missed the dose of the treatment, simulations were used to evaluate reinitiation treatment in patients who had missed a week 4 dose of paliperidone palmitate and returned to treatment at weeks 5, 6, 7 or 8. The simulations were also used to evaluate re-initiation treatment in patients who had a prolonged lapse of more than about 6 months. The patient may be administered a single dose at day 1 using the maintenance one that would have been administered at exactly the 4<sup>th</sup> week, or two doses at day 1/day 8 using the same dose as the maintenance dose. Both possibilities were investigated for the about 5, 6, 7, and 8 week scenarios using the doses of about 39, 78, 117, 156, and 234 mg of paliperidone palmitate. The time point at which re-initiation with 2 doses could be appropriate was judged based on visual inspection of simulated curves. The profiles after a missed dose were assessed empirically and proximity to the steady-state levels was the criterion for judging the utility of these dosing schemes.

[0089] These results in FIGS. 2 to 4 indicated that the reinitiation treatment after patients missed their Week 4 maintenance dose or the stabilized dose, re-initiation depended upon the time lapse since the last injection. For example, patients who missed their week 4 maintenance dose and returned to re-initiation at week 5 or 6 (i.e., time lapse since last injection is more than about 4 weeks and less than about 6 weeks) may be administered with single re-initiation dose at the previously stabilized dose followed by monthly injections (FIGS. 2 and 3). The doses may be administered in either the deltoid muscle with a 1.0 inch 23-G needle for the patients weighting less than about 90 kg or a 1.5 inch 22-G for those weighting equal or more than about 90 kg, or the gluteal muscle with a 1.5-inch 22-G needle for all weights. Additionally, [FIG. 6, Panel A and B] This is recommended as the models showed that reinitiation with two doses at day 1/day 8 resulted in a higher than desired plasma concentration (FIG. 3).

MYL-PP3M056060

PTX-116

PTX-0116\_0017



US 2011/0105536 A1

May 5, 2011

11

[0090] The simulations also showed that patients who missed their week 4 maintenance dose and returned to re-initiation at week 7 or 8 (i.e., time lapse since last injection is more than about 6 weeks and less than about 6 months) may be administered with two re-initiation doses at the previously stabilized dose followed by monthly injections. The two doses at day 1/day 8 allow re-attainment of steady-state plasma concentration quickly (FIG. 3). Additionally, the two reinitiation doses were injected into the deltoid muscle with a 1.0 inch 23-G needle for the patients weighting less than about 90 kg or a 1.5 inch 22-G for those weighting equal or more than about 90 kg. Each of the two re-initiation doses was the previously stabilized dose, except when the patient was stabilized on a dose of about 234 mg. For the patient stabilized on a dose of about 234 mg of paliperidone palmitate, the model recommended each of the first two doses of about 156 mg of paliperidone palmitate.

[0091] The simulations further recommended that patient who missed their week 4 maintenance dose and returned more than about 6 months were required to re-initiate the treatment de novo (FIG. 4). That is, patients were administered with paliperidone palmitate of about 234 mg on day 1 and about 156 mg on day 8. Each dose was administered into the deltoid muscle with needle selection based upon patient weight as discussed above. The re-initiation doses were followed by monthly paliperidone palmitate injections using maintenance dose recommendations as discussed above. Finally, the simulation models indicated that there is a  $\pm 2$  day dosing window for the administration of the second dose, if needed, and a  $\pm 7$  day dosing window for the administration of the monthly maintenance doses (data not shown).

#### Example 3

##### Switch Treatment from Oral Antipsychotic

[0092] Pharmacokinetic models or simulations were developed to examine drug levels when patients were switched from extended release (ER) oral paliperidone to paliperidone palmitate. The models also determined whether previous oral antipsychotics such as paliperidone ER could be discontinued at the time of initiation of treatment with paliperidone palmitate.

[0093] The models examined patients who were treated with a daily dosing of about 6 mg paliperidone ER and initiated with paliperidone palmitate on the first day after the last oral dose of paliperidone ER. The simulated concentrations of paliperidone from its palmitate ester were added to the drug levels from paliperidone ER using the superposition principles. The simulation models analyzed two scenarios: (A) patients switched from the dose of about 6 mg paliperidone ER to paliperidone palmitate using the two initiation doses of about 150 mg-eq. in the deltoid muscle on treatment day 1 and about 100 mg-eq. in the deltoid muscle one week later; and (B) patients switched from the dose of about 6 mg paliperidone ER to paliperidone palmitate using a single day 1 injection of about 150 mg-eq. dose. The results of the simulations were summarized in FIG. 5.

[0094] As shown in FIG. 5A, the desired paliperidone plasma levels were maintained during the first week of the switching treatment from about 6 mg paliperidone ER to day 1/day 8 initiation regimen of paliperidone palmitate. Though the paliperidone plasma levels decline rapidly from the oral treatment, the plasma levels or concentration increased due to the intramuscular administering of paliperidone palmitate at

day 1. Afterward, the administration of the 2<sup>nd</sup> dose of about 100 mg-eq. dose on day 8 maintained the drug levels in the desired therapeutic range.

[0095] On the contrary, the results of FIG. 5B showed that when the day 8 injection was skipped, the paliperidone plasma levels began to decline and became lower than the desired therapeutic range at about 2 weeks after the day 1 injection. Therefore, the initiation regimen of day 1/day 8 of paliperidone palmitate provided an effective treatment for switching patients from oral antipsychotics.

[0096] In addition to the simulation based analysis, a literature search was performed to evaluate the pharmacokinetic characteristics of other oral antipsychotics. The results of literature search for typical and atypical antipsychotics were summarized in Tables 1 and 2, respectively.

TABLE 1

Terminal Half-life of Oral Typical Antipsychotics

Oral Typical Antipsychotic	Terminal Half-life
Chlorpromazine	8-35 hours <sup>a</sup>
Flupenthixol	22-36 hours <sup>a</sup>
Fluphenazine	14-24 hours <sup>a</sup>
Haloperidol	12-36 hours <sup>a</sup>
Loxapine	4 hours <sup>b</sup>
Molindone	1.5 hours <sup>b</sup>
Perphenazine	8-21 hours <sup>a</sup>
Pimozide	2-3 days <sup>b</sup>
Prochlorperazine	4-8 hours <sup>b</sup>
Thioridazine	9-30 hours <sup>a</sup>
Thiothixene	34 hours <sup>a</sup>
Trifluoperazine	10-20 hours <sup>b</sup>

<sup>a</sup> Ereshefsky L. Pharmacokinetics and drug interactions: update for new antipsychotics. *J Clin Psychiatry*. 1996; 57 Suppl 11: 12-25.

<sup>b</sup> "Typical antipsychotic" in Wikipedia: The Free Encyclopedia, Wikimedia Foundation Inc [Encyclopedia on-line]; retrieved Aug. 6, 2009.

TABLE 2

Terminal Half-life of Oral Atypical Antipsychotics

Oral Atypical Antipsychotic	Terminal Half-life
Amisulpride	12 hours <sup>c</sup>
Aripiprazole	47-68 hours <sup>c</sup>
Clozapine	9-17 hours <sup>c</sup>
Olanzapine	33 hours <sup>c</sup>
Paliperidone (9-hydroxy-risperidone)	25 hours <sup>d</sup>
Quetiapine	6 hours <sup>e</sup>
Risperidone active moiety <sup>e</sup>	22 hours <sup>e</sup>
Sertindole	70 hours <sup>e</sup>
Ziprasidone	8-10 hours <sup>e</sup>

<sup>c</sup> Mauri M C, Volonterio L S, Colasanti A, Fiorentini A, De Gaspari I F, Bareggi S R. Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. *Clin Pharmacokinet*. 2007; 46(5): 359-88.

<sup>d</sup> Vermeir M, Naessens I, Remmerie B, Mannens G, Hendrickx J, Sterkens P, Talhouri K, Boon S, Eerdeleers M, van Oysel A, Cleton A. Absorption, metabolism, and excretion of paliperidone, a new monoaminergic antagonist, in humans. *Drug Metab Dispos*. 2008 April; 36(4): 769-79.

<sup>e</sup> Active moiety is the sum of parent drug plus its active metabolite 9-hydroxy-risperidone

[0097] As shown in the tables, all oral antipsychotics have half-life of less than about 3 days. Given the short half-life of the oral antipsychotics, the drug levels of the previous oral antipsychotic would be decline rapidly during the first week of initiation with paliperidone palmitate. Additionally, more than about 75% of the drug from the oral therapy would be washed out from the systemic circulation within the first week. These results further supported the simulations that a second loading dose of paliperidone palmitate after 7 days or

MYL-PP3M056061

PTX-116

PTX-0116\_0018

US 2011/0105536 A1

May 5, 2011

12

on the 8<sup>th</sup> day after the treatment day 1 would attain the paliperidone concentrations within the desired therapeutic range.

#### Example 4

##### Switch Treatment from Other Long Acting Injectable Antipsychotic

[0098] Pharmacokinetic models or simulations were also developed to examine the drug levels when patients were switched from RISPERDAL® CONSTA® to paliperidone palmitate. The modeling also determined whether the treatment with paliperidone palmitate could be initiated at the next scheduled injection of other injectable antipsychotic such as RISPERDAL® CONSTA®.

[0099] The models examined patients who were treated with a bi-weekly administration schedule of RISPERDAL® CONSTA® and switched to paliperidone palmitate for about two weeks after their last RISPERDAL® CONSTA® injection. The simulated concentrations of paliperidone from its palmitate ester were added to the active moiety profile from RISPERDAL® CONSTA® using the superposition principles, as RISPERDAL® CONSTA® has the same active moiety as paliperidone palmitate.

[0100] Plasma concentrations were simulated with paliperidone palmitate injection at about two weeks after the last RISPERDAL® CONSTA® injection followed by monthly injections of paliperidone palmitate. The simulation models analyzed two scenarios: (A) a low dose scenario where patients were switched from about 25 mg RISPERDAL® CONSTA® to about 50 mg-eq. paliperidone palmitate followed by monthly injections of about 50 mg-eq. paliperidone palmitate; and (B) a high dose scenario where patients were switched from about 50 mg RISPERDAL® CONSTA® to about 100 mg-eq. paliperidone palmitate followed by monthly injections of about 100 mg eq. paliperidone palmitate. These results were summarized in FIG. 6.

[0101] FIG. 6 showed that, for both low and high dose cases, the drug levels were maintained close to the steady-state concentrations right after the switch from RISPERDAL® CONSTA® to paliperidone palmitate. Additionally, after the last injection of RISPERDAL® CONSTA®, the steady state concentrations were maintained for about 4-5 weeks and declined thereafter with a mean plasma half-life of about 4-6 days. Therefore, at the time of switching treatment, only a single injection of paliperidone palmitate was sufficient. This simulation indicated that when switching patients from previous treatment of other long-acting injectable antipsychotics, paliperidone palmitate therapy may be initiated in place of the next scheduled injection and continued at monthly intervals. Also, the simulation indicated that the second dose of initiation dosing regimen and oral supplement were not required when switching from other long acting injectable antipsychotics.

[0102] In addition to the simulation based analysis, a literature search was conducted to evaluate the pharmacokinetic characteristics of other long acting injectable antipsychotics. The results were summarized in Table 3.

TABLE 3

Summary of the properties of depot intramuscular antipsychotics		
Drug	Administration interval	t <sub>1/2</sub> <sup>d</sup>
Clophenxol decanoate <sup>a</sup>	2-4 weeks	19 days
Perphenazine enanthate <sup>a</sup>	2 weeks	4-6 days
Pipothiazine palmitate <sup>a</sup>	4 weeks	15-16 days
Haloperidol decanoate <sup>a</sup>	4 weeks	21 days
Fluspirilene <sup>a</sup>	1 week	7 days
Zuclopenthixol decanoate <sup>a</sup>	2-4 weeks	19 days
Flupenthixol decanoate <sup>b</sup>	2-4 weeks	17 days
Fluphenazine decanoate <sup>b</sup>	2-5 weeks	14 days
Fluphenazine enanthate <sup>c</sup>	1 week	4 days
Risperidone Microspheres <sup>d</sup>	2 weeks	4-6 days
Olanzapine pamoate <sup>e</sup>	2-4 weeks	30 days

<sup>a</sup>Altamura A C, Sassella F, Santini A, Montresor C, Fumagalli S, Mundo E. Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. *Drugs*. 2003; 63(5): 493-512.

<sup>b</sup>Kane JM, Aguglia E, Altamura A C, Ayuso Gutierrez J L, Brunello N, Fleischacker W W, Gaebel W, Gerlach J, Guelfi J D, Kissling W, Lapiere Y D, Lindström E, Mendlewicz J, Raosni G, Carulla L S, Schooler N R. Guidelines for depot antipsychotic treatment in schizophrenia. *European Neuropsychopharmacology Consensus Conference in Siena, Italy*. *Eur Neuropsychopharmacol*. 1998; 8(1): 55-66.

<sup>c</sup>Levron J C, Ropert R. Clinical pharmacokinetics of haloperidol decanoate. Comparison with other prolonged-action neuroleptics. *Encephale*. 1987; 13(2): 83-7.

<sup>d</sup>Gefvert O, Eriksson B, Persson P, Helledin L, Björner A, Mannert E, Remmerie B, Eerdeken M, Nyberg S. Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta) in patients with schizophrenia. *Int J Neuropsychopharmacol*. 2005; 8(1): 27-36.

<sup>e</sup>Eli Lilly. Zypadhera. Summary of product characteristics. The Netherlands: Eli Lilly Nederland B. V. 2008. Available Online at: <http://www.emea.europa.eu/humandocs/PDFs/EPAR/Zypadhera/H-890-PI-en.pdf>. Accessed Sep. 1, 2009.

<sup>f</sup>t<sub>1/2</sub> = apparent terminal half-life after multiple dosing

[0103] The results in Table 3 showed that, for all depot antipsychotics, the administration interval was in the range of about 1-2 half-life for each product. Based on the simple first-order elimination pharmacokinetic principles, it may take about 4 to 5 half-life for such drugs to be eliminated from the systemic circulation. Therefore, there would be sustained therapeutic levels of the prior drug in the systemic circulation when paliperidone palmitate is administered in place of the next scheduled injection of the previous antipsychotic. Given that significant levels of the previous antipsychotic would be present in the systematic circulation, there would be no need to use the 2<sup>nd</sup> initiation dose of paliperidone palmitate on day 8.

What is claimed is:

1. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with a monthly injectable paliperidone palmitate depot, wherein said patient misses the next scheduled maintenance dose of the monthly injectable paliperidone palmitate depot, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of the monthly injectable paliperidone palmitate depot; and
- (2) administering intramuscularly in the deltoid or gluteal muscle of said patient a reinitiation maintenance dose of the monthly injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of said first reinitiation loading dose.

2. The method of claim 1, further comprising administering in the deltoid or gluteal muscle of said patient said reinitiation maintenance dose monthly.

3. The method of claim 1, wherein said patient misses the next scheduled maintenance dose of the monthly injectable paliperidone palmitate depot for more than about 4 weeks and less than about 6 weeks.

MYL-PP3M056062

PTX-116

PTX-0116\_0019

US 2011/0105536 A1

May 5, 2011

13

4. The method of claim 1, wherein said patient misses the next scheduled maintenance dose of the monthly injectable paliperidone palmitate depot for more than about 6 weeks and less than about 6 months.

5. The method of claim 1, wherein said patient misses the next scheduled maintenance dose of the monthly injectable paliperidone palmitate depot for more than about 6 months.

6. The method of claim 3, wherein said first reinitiation loading dose is the same amount as said scheduled maintenance dose.

7. The method of claim 3, wherein said first reinitiation loading dose is about 39 mg to about 234 mg.

8. The method of claim 3, wherein said reinitiation maintenance loading dose is about 39 to about 234 mg.

9. The method of claim 3, wherein said patient is in need of treatment for psychosis.

10. The method of claim 3, wherein said patient is in need of treatment for schizophrenia.

11. The method of claim 3, wherein said patient is in need of treatment for bipolar disorder.

12. The method of claim 4, further comprising administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation loading dose of the monthly injectable paliperidone palmitate depot on about the 6th day to about the 10th day after administering of said first reinitiation loading dose.

13. The method of claim 12, further comprising administering in the deltoid or gluteal muscle of said patient said reinitiation maintenance dose monthly.

14. The method of claim 12, wherein said first reinitiation loading dose is about 39 mg to about 117 mg.

15. The method of claim 12, wherein said second reinitiation loading dose is about 39 mg to about 117 mg.

16. The method of claim 5, further comprising administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation loading dose of the monthly

injectable paliperidone palmitate depot on about the 6th day to about the 10th day after administering of said first reinitiation loading dose.

17. The method of claim 16, further comprising administering in the deltoid or gluteal muscle of said patient said reinitiation maintenance dose monthly.

18. The method of claim 16, wherein said first reinitiation loading dose is about 39 mg to about 117 mg.

19. The method of claim 16, wherein said second reinitiation loading dose is about 39 mg to about 117 mg.

20. A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with injectable antipsychotic drugs other than paliperidone palmitate, wherein said patient is switched from said injectable antipsychotic drugs to injectable paliperidone palmitate depot, comprising:

(1) administering intramuscularly in the deltoid muscle of said patient a first loading dose of said injectable paliperidone palmitate depot; and

(2) administering intramuscularly in the deltoid or gluteal muscle of said patient a maintenance dose of said injectable paliperidone palmitate depot on about the 23rd day to about the 37th day after administering of said first reinitiation loading dose.

21. The method of claim 20, further comprising administering in the deltoid or gluteal muscle of said patient said maintenance dose monthly.

22. The method of claim 20, wherein said first loading dose is about 78 mg to about 234 mg.

23. The method of claim 20, wherein said maintenance dose is about 39 mg to about 234 mg.

24. The method of claim 20, wherein said patient is in need of treatment for psychosis.

25. The method of claim 20, wherein said patient is in need of treatment for schizophrenia.

26. The method of claim 20, wherein said patient is in need of treatment for bipolar disorder.

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## ORIGINAL RESEARCH ARTICLE

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# Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia

## A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic

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### Abstract

**Objectives:** To characterize the population pharmacokinetics of paliperidone after intramuscular administration of its long-acting palmitate ester at various doses and at two different injection sites (deltoid and gluteal muscle).

**Methods:** The retrospective analysis included pooled data from 1795 subjects from six phase I trials and five phase II and III trials. A total of 18 530 pharmacokinetic samples with valid concentration timepoints were available for this analysis. Nonlinear mixed-effects modelling of the pooled data was conducted using NONMEM® software. The full dataset was divided into an index dataset (model development) and a validation dataset. After validation both the index and validation datasets were combined and the final model was re-run on the full dataset.

**Results:** The concentration-time data for paliperidone following intramuscular administration of its palmitate ester were best fitted to a one-compartment model with first-order elimination. The absorption component of the model allowed a fraction of the dose ( $f_2$ ) to enter relatively quickly into the central compartment via a zero-order process. After a lag time, the remaining fraction then entered the systemic circulation via a first-order process. Interindividual variability (IIV) in clearance (CL), central volume of distribution ( $V_d$ ) and the absorption rate constant ( $k_a$ ) were estimated at a 40%, 69% and 59% coefficient of variation (CV), respectively. The IIV on  $f_2$  for paliperidone absorption via the dual-input process was fitted through logit transformation, and its standard deviation (SD) was 0.064. Similarly, the interoccasion variability (IOV) on CL,  $V_d$  and  $f_2$  was 26% CV, 14% CV and 0.07 SD, respectively. An additive-error model with log-transformed data was used to describe the residual variability (RV), and its SD was 0.22. The final covariate model indicated that the following variables had a significant influence on  $k_a$ : sex, age, injection volume (IVOL) and injection site (INJS). Similarly, the following variables had a significant influence on  $f_2$ : sex, body mass index (BMI), needle length (NDLL), INJS and IVOL. In addition, CL was related to creatinine clearance ( $CL_{CR}$ ), whereas  $V_d$  was related to BMI and sex.

**Conclusions:** A dual-absorption pharmacokinetic model best described the complex pharmacokinetics of paliperidone after intramuscular administration of its palmitate ester. These results suggest that the pharmacokinetics of paliperidone palmitate are mostly influenced by BMI,  $CL_{CR}$ , INJS, IVOL and NDLL.

### Background

Atypical antipsychotic agents represent a treatment option for many patients with schizophrenia.<sup>[1,2]</sup> Compliance with oral antipsychotic medications is particularly problematic for patients with schizophrenia and can correlate with poor out-

comes.<sup>[1,3-6]</sup> In part, to address this problem, sustained-release intramuscular formulations of older 'typical' antipsychotics, such as haloperidol and fluphenazine, were developed.

Paliperidone (9-hydroxy-risperidone) is an atypical antipsychotic agent and is the major active metabolite of risperidone with a receptor-binding profile similar to that of risperidone.

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Drug-drug interaction studies suggest that paliperidone, because of its predominant renal route of elimination, is not expected to exhibit clinically significant pharmacokinetic interactions, except with drugs that interact at the level of the kidney. In order to rapidly achieve therapeutic steady-state concentrations, two formulations of paliperidone have been developed: paliperidone extended release (ER) tablets, which use an oral ER osmotic pump technology (OROS®), and a long-acting injection, paliperidone palmitate, which is currently under investigation for the treatment of schizophrenia.<sup>[7]</sup> The US FDA approved Invega® Sustenna™ (paliperidone palmitate) extended-release injectable suspension for the acute and maintenance treatment of schizophrenia in adults on July 31, 2009.<sup>[8]</sup> Similarly, Invega® (oral paliperidone ER tablets) is approved for acute and maintenance treatment of schizophrenia and acute treatment of schizoaffective disorder either as monotherapy or adjunctive therapy to mood stabilizers and/or antidepressants.<sup>[9]</sup>

Because paliperidone is combined with other excipients in the injectable formulation, doses of paliperidone palmitate can be expressed in terms of milligram equivalents (mg eq.) of the active moiety, paliperidone. Thus, paliperidone palmitate 156 mg is equivalent to paliperidone 100 mg and is referred to as 100 mg eq.

Paliperidone palmitate was formulated as an aqueous suspension with a particle-size distribution that has sustained-release properties and thus facilitates once-monthly (every 4 weeks) dosing. Based on its extremely low water solubility, paliperidone palmitate dissolves slowly at the injection site after intramuscular injection and is then hydrolysed to paliperidone.<sup>[10]</sup> Once the ester is hydrolysed intramuscularly, paliperidone then becomes available in the systemic circulation.<sup>[10]</sup> Paliperidone palmitate provides relatively constant plasma concentrations of paliperidone and may offer both an alternative to daily oral dosing and an opportunity for enhanced compliance.

The purpose of this study was to characterize the population pharmacokinetics of paliperidone after intramuscular administration of its palmitate ester at various doses and at two different injection sites (deltoid and gluteal muscle).

## Methods

### Patient Population, Data Allocation, Bioanalysis and Clinical Formulations

All subjects in the phase II and III development programme met criteria for a *Diagnostic and Statistical Manual of Mental*

*Disorders* diagnosis of schizophrenia.<sup>[11]</sup> In phase I trials, subjects with similar psychotic disorders (e.g. schizophreniform or schizoaffective disorder) were allowed to participate and were therefore largely representative of the population studied in the phase III programme.

A total of 1795 subjects from 11 trials were included in the population pharmacokinetic analysis of paliperidone. All plasma samples with quantifiable concentrations of paliperidone, with date and time of sampling, including the last dose administration, were used for the population pharmacokinetic analysis. Measurements below the quantification limit and missing values were excluded from the analysis. Pharmacokinetic samples were analysed using a validated liquid chromatography coupled to tandem mass spectrometry method.<sup>[12]</sup>

Details of the 11 trials included in this analysis are presented in table I. The dosing regimen for multiple-dose trials (except Study INT-11) consisted of two initial intramuscular injections separated by 1 week, followed by subsequent doses at monthly (every 4 weeks) intervals. This is also the proposed recommended dosing regimen for the product that is to be marketed, and is based on the principle that this regimen allows faster attainment of apparent steady state, especially given the long apparent half-life of this product.

Six paliperidone palmitate phase I trials were available with sufficient information on the full plasma concentration-time profiles of paliperidone (n=459 subjects; 9935 pharmacokinetic samples). Pharmacokinetic information was also available from one phase II trial and four phase III trials. In total, 15 754 (85%) pharmacokinetic samples were used to develop the population pharmacokinetic model from 1401 (78.1%) subjects from nine trials, and this was referred to as the index dataset. The model was validated using an external dataset that consisted of data from one phase I (PSY-1002 trial) and one phase III (PSY-3002) trial. The validation studies included 394 (21.9%) subjects who contributed to 2776 (15%) plasma samples. Once the population pharmacokinetic model was validated, the index and validation datasets were combined, and the final model was re-run on the full dataset. The full dataset consisted of 18 530 samples from 1795 subjects.

Paliperidone palmitate was supplied as a sterile aqueous suspension (100 mg eq./mL) for intramuscular injections at doses of 25–150 mg eq. with injection volume (IVOL) varying from 0.25 mL to 1.5 mL. In the database, two different formulations, F011 and F013, were used by 684 and 1111 subjects, respectively. The population pharmacokinetic analysis was used to evaluate the similarity in pharmacokinetic parameters and systemic exposure between these two formulations.

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PTX-118



PTX-0133

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use **PALIPERIDONE PALMITATE EXTENDED-RELEASE INJECTABLE SUSPENSION** safely and effectively. See full prescribing information for **PALIPERIDONE PALMITATE EXTENDED-RELEASE INJECTABLE SUSPENSION**.

**PALIPERIDONE PALMITATE** extended-release injectable suspension, for intramuscular use  
Initial U.S. Approval: 2006

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Paliperidone palmitate is not approved for use in patients with dementia-related psychosis. (5.1)

**RECENT MAJOR CHANGES**

Warnings and Precautions (5.3, 5.5)

2/2021

**INDICATIONS AND USAGE**

Paliperidone palmitate extended-release injectable suspension, a 3-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in patients after they have been adequately treated with 1-month paliperidone palmitate extended-release injectable suspension for at least four months. (1)

**DOSAGE AND ADMINISTRATION**

- Use 3-month paliperidone palmitate extended-release injectable suspension only after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least four months. (2.2)
- Paliperidone palmitate extended-release injectable suspension should be administered once every 3 months. (2.1)
- For intramuscular injection only. (2.1)
- Each injection must be administered only by a healthcare professional. (2.1)
- For deltoid injection: For patients weighing less than 90 kg, use the 1-inch 22 gauge thin wall needle. For patients weighing 90 kg or more, use the 1½-inch 22 gauge thin wall needle.
- For gluteal injection: Regardless of patient weight, use the 1½-inch 22 gauge thin wall needle.
- Prior to administration, shake the prefilled syringe vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension. (2.1)
- Initiate 3-month paliperidone palmitate when the next 1-month paliperidone palmitate dose is scheduled with a 3-month paliperidone palmitate dose based on the previous 1-month injection dose as shown below. (2.2)

**3-Month Paliperidone Palmitate Extended-Release Injectable Suspension Doses for Adult Patients Adequately Treated with 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension**

If the Last Dose of 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension is:	Initiate 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension at the Following Dose:
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the paliperidone palmitate extended-release injectable suspension 39 mg dose was not studied.

- Missed Doses: Missing doses of paliperidone palmitate extended-release injectable suspension should be avoided. To manage missed doses on exceptional occasions, refer to the Full Prescribing Information. (2.3)
- Moderate to severe renal impairment (creatinine clearance < 50 mL/min): Paliperidone palmitate extended-release injectable suspension is not recommended. (2.5)

- Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Adjust dosage and stabilize the patient using 1-month paliperidone palmitate extended-release injectable suspension, then transition to 3-month paliperidone palmitate extended-release injectable suspension. See above table. (2.5)

**DOSAGE FORMS AND STRENGTHS**

Extended-release injectable suspension: 819 mg (3)

**CONTRAINDICATIONS**

Known hypersensitivity to paliperidone, risperidone, or to any excipients in paliperidone palmitate extended-release injectable suspension. (4)

**WARNINGS AND PRECAUTIONS**

- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:** Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). Paliperidone palmitate extended-release injectable suspension is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation of drug and close monitoring (5.3)
- QT Prolongation:** Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)
- Tardive Dyskinesia:** Discontinue drug if clinically appropriate (5.5)
- Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
  - Hyperglycemia and Diabetes Mellitus:** Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
  - Dyslipidemia:** Undesirable alterations have been observed. (5.6)
  - Weight Gain:** Significant weight gain has been reported. Monitor weight gain. (5.6)
- Orthostatic Hypotension and Syncope:** Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis:** Monitor complete blood count in patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.9)
- Hyperprolactinemia:** Prolactin elevations occur and persist during chronic administration (5.10)
- Potential for Cognitive and Motor Impairment:** Use caution when operating machinery (5.11)
- Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.12)

**ADVERSE REACTIONS**

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

**Strong CYP3A4/P-glycoprotein (P-gp) inducers:** Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during a dosing interval for paliperidone palmitate extended-release injectable suspension. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets. (7.2, 12.3)

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)



## FULL PRESCRIBING INFORMATION

### **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Paliperidone palmitate is not approved for use in patients with dementia-related psychosis. [see Warnings and Precautions (5.1)].**

## **1 INDICATIONS AND USAGE**

Paliperidone palmitate extended-release injectable suspension, a 3-month injection, is indicated for the treatment of schizophrenia in patients after they have been adequately treated with 1-month paliperidone palmitate extended-release injectable suspension for at least four months [see Dosage and Administration (2.2) and Clinical Studies (14)].

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Administration Instructions**

Paliperidone palmitate extended-release injectable suspension should be administered once every 3 months.

Each injection must be administered only by a healthcare professional.

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration. **It is important to shake the syringe vigorously for at least 15 seconds to ensure a homogeneous suspension. Inject paliperidone palmitate extended-release injectable suspension within 5 minutes of shaking vigorously [see Dosage and Administration (2.8)].**

Paliperidone palmitate extended-release injectable suspension is intended for intramuscular use only. Do not administer by any other route. Avoid inadvertent injection into a blood vessel. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the deltoid or gluteal muscle.

Paliperidone palmitate extended-release injectable suspension must be administered using only the thin wall needles that are provided in the 3-month paliperidone palmitate extended-release injectable suspension pack. Do not use needles from the 1-month paliperidone palmitate extended-release injectable suspension pack or other commercially-available needles to reduce the risk of blockage.

#### **Deltoid Injection**

The recommended needle size for administration of paliperidone palmitate extended-release injectable suspension into the deltoid muscle is determined by the patient's weight:

- For patients weighing less than 90 kg, the 1-inch, 22 gauge thin wall needle is recommended.
- For patients weighing 90 kg or more, the 1½-inch, 22 gauge thin wall needle is recommended.

Administer into the center of the deltoid muscle. Deltoid injections should be alternated between the two deltoid muscles.

#### Gluteal Injection

Regardless of patient weight, the recommended needle size for administration of paliperidone palmitate extended-release injectable suspension into the gluteal muscle is the 1½-inch, 22 gauge thin wall needle. Administer into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be alternated between the two gluteal muscles.

#### Incomplete Administration

To avoid an incomplete administration of paliperidone palmitate extended-release injectable suspension, ensure that the prefilled syringe is **shaken vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension and ensure the needle does not get clogged during injection** [see *Dosage and Administration* (2.8)].

However, in the event of an incompletely administered dose, do **not** re-inject the dose remaining in the syringe and do **not** administer another dose of paliperidone palmitate extended-release injectable suspension. Closely monitor and treat the patient with oral supplementation as clinically appropriate until the next scheduled 3-month injection of paliperidone palmitate extended-release injectable suspension.

## 2.2 Schizophrenia

### Adults

3-month paliperidone palmitate extended-release injectable suspension is to be used only after 1-month paliperidone palmitate extended-release injectable suspension has been established as adequate treatment for at least four months. In order to establish a consistent maintenance dose, it is recommended that the last two doses of 1-month paliperidone palmitate extended-release injectable suspension be the same dosage strength before starting 3-month paliperidone palmitate extended-release injectable suspension.

Initiate 3-month paliperidone palmitate extended-release injectable suspension when the next 1-month paliperidone palmitate dose is scheduled with a 3-month paliperidone palmitate dose based on the previous 1-month injection dose, using the equivalent 3.5-fold higher dose as shown in Table 1. Paliperidone palmitate extended-release injectable suspension may be administered up to 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.

**Table 1. 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension Doses for Adult Patients Adequately Treated with 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension**

<b>If the Last Dose of 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension is:</b>	<b>Initiate 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension at the Following Dose:</b>
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the paliperidone palmitate extended-release injectable suspension 39 mg dose was not studied.

Following the initial paliperidone palmitate extended-release injectable suspension dose, paliperidone palmitate extended-release injectable suspension should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 273 mg to 819 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of paliperidone palmitate extended-release injectable suspension, the patient's response to an adjusted dose may not be apparent for several months [*see Clinical Pharmacology (12.3)*].

## **2.3 Missed Doses**

### **Dosing Window**

Missing doses of paliperidone palmitate extended-release injectable suspension should be avoided. If necessary, patients may be given the injection up to 2 weeks before or after the 3-month time point.

### **Missed Dose 3½ Months to 4 Months Since Last Injection**

If more than 3½ months (up to but less than 4 months) have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, the previously administered paliperidone palmitate extended-release injectable suspension dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

### **Missed Dose 4 Months to 9 Months Since Last Injection**

If 4 months up to and including 9 months have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, do NOT administer the next dose of paliperidone palmitate extended-release injectable suspension. Instead, use the re-initiation regimen shown in Table 2.

**Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of Paliperidone Palmitate Extended-Release Injectable Suspension**

If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension was:	Administer 1-month paliperidone palmitate extended-release injectable suspension, two doses one week apart (into deltoid muscle)		Then administer 3-month paliperidone palmitate extended-release injectable suspension (into deltoid <sup>a</sup> or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

<sup>a</sup> See Instructions for Use for deltoid injection needle selection based on body weight.

#### Missed Dose Longer than 9 Months Since Last Injection

If more than 9 months have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, re-initiate treatment with the 1-month paliperidone palmitate extended-release injectable suspension as described in the prescribing information for that product. 3-month paliperidone palmitate extended-release injectable suspension can then be resumed after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least 4 months.

#### 2.4 Use with Risperidone or with Oral Paliperidone

Since paliperidone is the major active metabolite of risperidone, caution should be exercised when paliperidone palmitate extended-release injectable suspension is coadministered with risperidone or oral paliperidone for extended periods of time. Safety data involving concomitant use of paliperidone palmitate extended-release injectable suspension with other antipsychotics is limited.

#### 2.5 Dosage Adjustment in Renal Impairment

Paliperidone palmitate extended-release injectable suspension has not been systematically studied in patients with renal impairment [see *Clinical Pharmacology* (12.3)]. For patients with mild renal impairment (creatinine clearance  $\geq 50$  mL/min to  $< 80$  mL/min [Cockcroft-Gault Formula]), adjust dosage and stabilize the patient using the 1-month paliperidone palmitate extended-release injectable suspension, then transition to 3-month paliperidone palmitate extended-release injectable suspension [see *Table 1, Dosage and Administration* (2.2)]. [See also *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)]

Paliperidone palmitate extended-release injectable suspension is not recommended in patients with moderate or severe renal impairment (creatinine clearance  $< 50$  mL/min) [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

## 2.6 Switching from 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension to the 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension

For switching from 3-month paliperidone palmitate extended-release injectable suspension to 1-month paliperidone palmitate extended-release injectable suspension, the 1-month paliperidone palmitate extended-release injectable suspension should be started 3 months after the last paliperidone palmitate extended-release injectable suspension dose, using the equivalent 3.5-fold lower dose as shown in Table 3. The 1-month paliperidone palmitate extended-release injectable suspension should then continue, dosed at monthly intervals.

**Table 3. Conversion From 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension to 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension**

<b>If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension is:</b>	<b>Initiate<sup>a</sup> 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension 3 Months Later at the Following Dose:</b>
273 mg	78 mg
410 mg	117 mg
546 mg	156 mg
819 mg	234 mg

<sup>a</sup> The initiation dosing as described in the prescribing information for 1-month paliperidone palmitate extended-release injectable suspension is not required

## 2.7 Switching from 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension to Oral Paliperidone Extended-Release Tablets

For switching from 3-month paliperidone palmitate extended-release injectable suspension to oral paliperidone extended-release tablets, the daily dosing of the paliperidone extended-release tablets should be started 3 months after the last paliperidone palmitate extended-release injectable suspension dose and transitioned over the next several months following the last paliperidone palmitate extended-release injectable suspension dose as described in Table 4. Table 4 provides dose conversion regimens to allow patients previously stabilized on different doses of paliperidone palmitate extended-release injectable suspension to attain similar paliperidone exposure with once daily paliperidone extended-release tablets.

**Table 4. Paliperidone Palmitate Extended-Release Injectable Suspension Doses and Once-Daily Paliperidone Extended-Release Conversion Regimens Needed to Attain Similar Paliperidone Exposures**

	<b>Weeks Since Last Paliperidone Palmitate Extended-Release Injectable Suspension Dose</b>		
	<b>3 months to 18 weeks</b>	<b>Longer than 18 weeks to 24 weeks</b>	<b>Longer than 24 weeks</b>
<b>Last Paliperidone Palmitate Extended-Release Injectable Suspension Dose</b>	<b>Doses of oral paliperidone extended-release tablets</b>		
273 mg	3 mg	3 mg	3 mg
410 mg	3 mg	3 mg	6 mg
546 mg	3 mg	6 mg	9 mg



PTX-0162

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use **PALIPERIDONE PALMITATE EXTENDED-RELEASE INJECTABLE SUSPENSION** safely and effectively. See full prescribing information for **PALIPERIDONE PALMITATE EXTENDED-RELEASE INJECTABLE SUSPENSION**.

**PALIPERIDONE PALMITATE** extended-release injectable suspension, for intramuscular use  
Initial U.S. Approval: 2006

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. **Paliperidone palmitate is not approved for use in patients with dementia-related psychosis. (5.1)**

**INDICATIONS AND USAGE**

Paliperidone palmitate extended-release injectable suspension, a 3-month injection, is an atypical antipsychotic indicated for the treatment of schizophrenia in patients after they have been adequately treated with 1-month paliperidone palmitate extended-release injectable suspension for at least four months. (1)

**DOSAGE AND ADMINISTRATION**

- ∞ Use 3-month paliperidone palmitate extended-release injectable suspension only after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least four months. (2.2)
- ∞ Paliperidone palmitate extended-release injectable suspension should be administered once every 3 months. (2.1)
- ∞ For intramuscular injection only. (2.1)
- ∞ Each injection must be administered only by a health care professional. (2.1)
- ∞ For deltoid injection: For patients weighing less than 90 kg, use the 1-inch 22 gauge thin wall needle. For patients weighing 90 kg or more, use the 1½-inch 22 gauge thin wall needle.
- ∞ For gluteal injection: Regardless of patient weight, use the 1½-inch 22 gauge thin wall needle.
- ∞ Prior to administration, shake the prefilled syringe vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension. (2.1)
- ∞ Initiate 3-month paliperidone palmitate when the next 1-month paliperidone palmitate dose is scheduled with a 3-month paliperidone palmitate dose based on the previous 1-month injection dose as shown below. (2.2)

**3-Month Paliperidone Palmitate Extended-Release Injectable Suspension Doses for Adult Patients Adequately Treated with 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension**

If the Last Dose of 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension is:	Initiate 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension at the Following Dose:
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the paliperidone palmitate extended-release injectable suspension 39 mg dose was not studied.

- ∞ Missed Doses: Missing doses of paliperidone palmitate extended-release injectable suspension should be avoided. To manage missed doses on exceptional occasions, refer to the Full Prescribing Information. (2.3)
- ∞ Moderate to severe renal impairment (creatinine clearance < 50 mL/min): Paliperidone palmitate extended-release injectable suspension is not recommended. (2.5)
- ∞ Mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min): Adjust dosage and stabilize the patient using 1-month paliperidone palmitate extended-release injectable suspension,

then transition to 3-month paliperidone palmitate extended-release injectable suspension. See above table. (2.5)

**DOSAGE FORMS AND STRENGTHS**

Extended-release injectable suspension: 546 mg (3)

**CONTRAINDICATIONS**

Known hypersensitivity to paliperidone, risperidone, or to any excipients in paliperidone palmitate extended-release injectable suspension. (4)

**WARNINGS AND PRECAUTIONS**

- ∞ **Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis:** Increased incidence of cerebrovascular adverse reactions (e.g. stroke, transient ischemic attack, including fatalities). Paliperidone palmitate extended-release injectable suspension is not approved for use in patients with dementia-related psychosis (5.2)
- ∞ **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation of drug and close monitoring (5.3)
- ∞ **QT Prolongation:** Avoid use with drugs that also increase QT interval and in patients with risk factors for prolonged QT interval (5.4)
- ∞ **Tardive Dyskinesia:** Discontinue drug if clinically appropriate (5.5)
- ∞ **Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include:
  - **Hyperglycemia and Diabetes Mellitus:** Monitor for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes. (5.6)
  - **Dyslipidemia:** Undesirable alterations have been observed. (5.6)
  - **Weight Gain:** Significant weight gain has been reported. Monitor weight gain. (5.6)
- ∞ **Orthostatic Hypotension and Syncope:** Use with caution in patients with known cardiovascular or cerebrovascular disease and patients predisposed to hypotension (5.7)
- ∞ **Leukopenia, Neutropenia, and Agranulocytosis:** Monitor complete blood count in patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.9)
- ∞ **Hyperprolactinemia:** Prolactin elevations occur and persist during chronic administration (5.10)
- ∞ **Potential for Cognitive and Motor Impairment:** Use caution when operating machinery (5.11)
- ∞ **Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.12)

**ADVERSE REACTIONS**

The most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo) were injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

**Strong CYP3A4/P-glycoprotein (P-gp) inducers:** Avoid using a strong inducer of CYP3A4 and/or P-gp (e.g., carbamazepine, rifampin, St John's Wort) during a dosing interval for paliperidone palmitate extended-release injectable suspension. If administering a strong inducer is necessary, consider managing the patient using paliperidone extended release tablets. (7.2, 12.3)

**USE IN SPECIFIC POPULATIONS**

**Pregnancy:** May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

## FULL PRESCRIBING INFORMATION

### **WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Paliperidone palmitate is not approved for use in patients with dementia-related psychosis. [see Warnings and Precautions (5.1)].**

## **1 INDICATIONS AND USAGE**

Paliperidone palmitate extended-release injectable suspension, a 3-month injection, is indicated for the treatment of schizophrenia in patients after they have been adequately treated with 1-month paliperidone palmitate extended-release injectable suspension for at least four months [see Dosage and Administration (2.2) and Clinical Studies (14)].

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Administration Instructions**

Paliperidone palmitate extended-release injectable suspension should be administered once every 3 months.

Each injection must be administered only by a health care professional.

Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration. **It is important to shake the syringe vigorously for at least 15 seconds to ensure a homogeneous suspension. Inject paliperidone palmitate extended-release injectable suspension within 5 minutes of shaking vigorously** [see Dosage and Administration (2.8)].

Paliperidone palmitate extended-release injectable suspension is intended for intramuscular use only. Do not administer by any other route. Avoid inadvertent injection into a blood vessel. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the deltoid or gluteal muscle.

Paliperidone palmitate extended-release injectable suspension must be administered using only the thin wall needles that are provided in the 3-month paliperidone palmitate extended-release injectable suspension pack. Do not use needles from the 1-month paliperidone palmitate extended-release injectable suspension pack or other commercially-available needles to reduce the risk of blockage.

#### **Deltoid Injection**

The recommended needle size for administration of paliperidone palmitate extended-release injectable suspension into the deltoid muscle is determined by the patient's weight:

- For patients weighing less than 90 kg, the 1-inch, 22 gauge thin wall needle is recommended.
- For patients weighing 90 kg or more, the 1½-inch, 22 gauge thin wall needle is recommended.

Administer into the center of the deltoid muscle. Deltoid injections should be alternated between the two deltoid muscles.

#### Gluteal Injection

Regardless of patient weight, the recommended needle size for administration of paliperidone palmitate extended-release injectable suspension into the gluteal muscle is the 1½-inch, 22 gauge thin wall needle. Administer into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be alternated between the two gluteal muscles.

#### Incomplete Administration

To avoid an incomplete administration of paliperidone palmitate extended-release injectable suspension, ensure that the prefilled syringe is **shaken vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension and ensure the needle does not get clogged during injection** [see *Dosage and Administration* (2.8)].

However, in the event of an incompletely administered dose, do **not** re-inject the dose remaining in the syringe and do **not** administer another dose of paliperidone palmitate extended-release injectable suspension. Closely monitor and treat the patient with oral supplementation as clinically appropriate until the next scheduled 3-month injection of paliperidone palmitate extended-release injectable suspension.

## 2.2 Schizophrenia

### Adults

3-month paliperidone palmitate extended-release injectable suspension is to be used only after 1-month paliperidone palmitate extended-release injectable suspension has been established as adequate treatment for at least four months. In order to establish a consistent maintenance dose, it is recommended that the last two doses of 1-month paliperidone palmitate extended-release injectable suspension be the same dosage strength before starting 3-month paliperidone palmitate extended-release injectable suspension.

Initiate 3-month paliperidone palmitate extended-release injectable suspension when the next 1-month paliperidone palmitate dose is scheduled with a 3-month paliperidone palmitate dose based on the previous 1-month injection dose, using the equivalent 3.5-fold higher dose as shown in Table 1. Paliperidone palmitate extended-release injectable suspension may be administered up to 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.



**Table 1. 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension Doses for Adult Patients Adequately Treated with 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension**

<b>If the Last Dose of 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension is:</b>	<b>Initiate 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension at the Following Dose:</b>
78 mg	273 mg
117 mg	410 mg
156 mg	546 mg
234 mg	819 mg

Conversion from the paliperidone palmitate extended-release injectable suspension 39 mg dose was not studied.

Following the initial paliperidone palmitate extended-release injectable suspension dose, paliperidone palmitate extended-release injectable suspension should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 273 mg to 819 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of paliperidone palmitate extended-release injectable suspension, the patient's response to an adjusted dose may not be apparent for several months [see *Clinical Pharmacology* (12.3)].

## **2.3 Missed Doses**

### **Dosing Window**

Missing doses of paliperidone palmitate extended-release injectable suspension should be avoided. If necessary, patients may be given the injection up to 2 weeks before or after the 3-month time point.

### **Missed Dose 3½ Months to 4 Months Since Last Injection**

If more than 3½ months (up to but less than 4 months) have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, the previously administered paliperidone palmitate extended-release injectable suspension dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

### **Missed Dose 4 Months to 9 Months Since Last Injection**

If 4 months up to and including 9 months have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, do NOT administer the next dose of paliperidone palmitate extended-release injectable suspension. Instead, use the re-initiation regimen shown in Table 2.

**Table 2. Re-initiation Regimen After Missing 4 Months to 9 Months of Paliperidone Palmitate Extended-Release Injectable Suspension**

If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension was:	Administer 1-month paliperidone palmitate extended-release injectable suspension, two doses one week apart (into deltoid muscle)		Then administer 3-month paliperidone palmitate extended-release injectable suspension (into deltoid <sup>a</sup> or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
273 mg	78 mg	78 mg	273 mg
410 mg	117 mg	117 mg	410 mg
546 mg	156 mg	156 mg	546 mg
819 mg	156 mg	156 mg	819 mg

<sup>a</sup> See Instructions for Use for deltoid injection needle selection based on body weight.

#### Missed Dose Longer than 9 Months Since Last Injection

If more than 9 months have elapsed since the last injection of paliperidone palmitate extended-release injectable suspension, re-initiate treatment with the 1-month paliperidone palmitate extended-release injectable suspension as described in the prescribing information for that product. 3-month paliperidone palmitate extended-release injectable suspension can then be resumed after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least 4 months.

#### 2.4 Use with Risperidone or with Oral Paliperidone

Since paliperidone is the major active metabolite of risperidone, caution should be exercised when paliperidone palmitate extended-release injectable suspension is coadministered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of paliperidone palmitate extended-release injectable suspension with other antipsychotics is limited.

#### 2.5 Dosage Adjustment in Renal Impairment

Paliperidone palmitate extended-release injectable suspension has not been systematically studied in patients with renal impairment [see *Clinical Pharmacology* (12.3)]. For patients with mild renal impairment (creatinine clearance  $\geq 50$  mL/min to  $< 80$  mL/min [Cockcroft-Gault Formula]), adjust dosage and stabilize the patient using the 1-month paliperidone palmitate extended-release injectable suspension, then transition to 3-month paliperidone palmitate extended-release injectable suspension [see *Table 1, Dosage and Administration* (2.2)]. [See also *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)]

Paliperidone palmitate extended-release injectable suspension is not recommended in patients with moderate or severe renal impairment (creatinine clearance  $< 50$  mL/min) [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

## 2.6 Switching from 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension to the 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension

For switching from 3-month paliperidone palmitate extended-release injectable suspension to 1-month paliperidone palmitate extended-release injectable suspension, the 1-month paliperidone palmitate extended-release injectable suspension should be started 3 months after the last paliperidone palmitate extended-release injectable suspension dose, using the equivalent 3.5-fold lower dose as shown in Table 3. The 1-month paliperidone palmitate extended-release injectable suspension should then continue, dosed at monthly intervals.

**Table 3. Conversion From 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension to 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension**

<b>If the Last Dose of 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension is:</b>	<b>Initiate<sup>a</sup> 1-Month Paliperidone Palmitate Extended-Release Injectable Suspension 3 Months Later at the Following Dose:</b>
273 mg	78 mg
410 mg	117 mg
546 mg	156 mg
819 mg	234 mg

<sup>a</sup> The initiation dosing as described in the prescribing information for 1-month paliperidone palmitate extended-release injectable suspension is not required

## 2.7 Switching from 3-Month Paliperidone Palmitate Extended-Release Injectable Suspension to Oral Paliperidone Extended-Release Tablets

For switching from 3-month paliperidone palmitate extended-release injectable suspension to oral paliperidone extended-release tablets, the daily dosing of the paliperidone extended-release tablets should be started 3 months after the last paliperidone palmitate extended-release injectable suspension dose and transitioned over the next several months following the last paliperidone palmitate extended-release injectable suspension dose as described in Table 4. Table 4 provides dose conversion regimens to allow patients previously stabilized on different doses of paliperidone palmitate extended-release injectable suspension to attain similar paliperidone exposure with once daily paliperidone extended-release tablets.

**Table 4. Paliperidone Palmitate Extended-Release Injectable Suspension Doses and Once-Daily Paliperidone Extended-Release Conversion Regimens Needed to Attain Similar Paliperidone Exposures**

	<b>Weeks Since Last Paliperidone Palmitate Extended-Release Injectable Suspension Dose</b>		
	<b>3 months to 18 weeks</b>	<b>Longer than 18 weeks to 24 weeks</b>	<b>Longer than 24 weeks</b>
<b>Last Paliperidone Palmitate Extended-Release Injectable Suspension Dose</b>	<b>Doses of oral paliperidone extended-release tablets</b>		
273 mg	3 mg	3 mg	3 mg
410 mg	3 mg	3 mg	6 mg
546 mg	3 mg	6 mg	9 mg



# Baseline characteristics and treatment patterns of patients with schizophrenia initiated on once-every-three-months paliperidone palmitate in a real-world setting

Kruti Joshi, Marie-Hélène Lafeuille, Brianne Brown, Willy Wynant, Bruno Emond, Patrick Lefebvre & Neeta Tandon

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## ORIGINAL ARTICLE



## Baseline characteristics and treatment patterns of patients with schizophrenia initiated on once-every-three-months paliperidone palmitate in a real-world setting

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### ABSTRACT

**Objectives:** Since May 2015, adult patients with schizophrenia adequately treated with once monthly paliperidone palmitate (PP1M) may be transitioned to once-every-three-months paliperidone palmitate (PP3M). This study aims to describe baseline characteristics and treatment patterns of patients with schizophrenia initiated on PP3M in a real-world setting.

**Methods:** Pharmacy and medical claims from May 2014 to September 2016 for adult patients with schizophrenia initiated on PP3M (index date) in the Symphony Health Solutions database were analyzed. The cohort consisting of all patients and the one restricted to those transitioning from PP1M as per prescribing guideline recommendations were considered. Baseline characteristics were assessed during the 12 month baseline period. PP1M treatment patterns, proportion of days covered (PDC) by mental-health-related medications, and healthcare resource utilization (HRU) patterns were evaluated for each baseline quarter. PP3M treatment patterns were assessed post-index.

**Results:** Among the 1545 adult patients initiated on PP3M who formed the first cohort, 68.8% transitioned from PP1M based on prescribing guidelines and on an adaptation of the strict clinical trial protocol for PP1M to PP3M transition, forming the second cohort. In both cohorts, the proportion of patients with a PDC  $\geq 80\%$  for antipsychotics, antidepressants, anxiolytics, and mood stabilizers increased while the proportion of patients with  $\geq 1$  emergency room, inpatient, or outpatient visit decreased in baseline quarters closer to PP3M initiation. Among patients with  $\geq 4$  months of follow-up after the first dose, 85–88% had a second dose. Similarly, among those with  $\geq 4$  months of follow-up after the second dose, 87–90% received a third dose.

**Conclusions:** Patients initiated on PP3M demonstrated decreased HRU and increased adherence in quarters closer to PP3M initiation, and were persistent on their PP3M treatment.

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Paliperidone palmitate; schizophrenia; adherence; healthcare resource utilization; treatment patterns

### Introduction

Schizophrenia is a severe mental illness characterized by a breakdown of thought processes, poor emotional responsiveness, and symptoms such as hallucinations and delusions<sup>1</sup>. It ranks among the top 10 causes of disability in developed countries worldwide<sup>2</sup> and is associated with a significant economic burden estimated at \$155.7 billion in 2013<sup>3</sup>. While direct healthcare costs represent almost 25% of this burden, non-healthcare costs and indirect costs such as unemployment are important contributors<sup>3</sup>. Following a first episode, 85%–90% of patients experience further episodes<sup>4</sup> whereas, with each relapse, remission of symptoms may be slower and the course of illness worse<sup>5,6</sup> highlighting the need for effective treatments.

Antipsychotics (APs) are the mainstay pharmacologic treatment for patients with schizophrenia. The chronic nature of the disease means that most patients require lifelong AP medications and their consistent use is the leading

determinant of effective management of schizophrenia symptoms and relapse control<sup>7</sup>. However, adherence to AP medication has already been shown to be poor<sup>8–11</sup>. Nonadherence to medication has a negative impact on the course of illness, resulting in relapse, rehospitalization, longer time to remission, and attempted suicide, all of which contribute to the already high costs of the disease to healthcare systems<sup>12–16</sup>.

It has been shown that reduced dosing frequency improves adherence in chronic diseases<sup>17–22</sup>. For example, among Medicaid patients with history of non-adherence before a schizophrenia-related hospitalization, those who received a long-acting injectable (LAI) within 30 days post-discharge were more likely to be adherent to their medication compared to those who received an oral AP<sup>23</sup>. Compared with the oral formulations, the LAI formulations of APs have the advantage of a sustained release profile and lower frequency of administration<sup>24</sup>. This eliminates the need for daily oral medication and could improve treatment adherence.

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Once monthly paliperidone palmitate (PP1M) is an atypical LAI for the maintenance treatment of schizophrenia in adults<sup>25</sup>. It has been associated with significant reductions in treatment nonadherence, treatment discontinuation, schizophrenia-related rehospitalization, and longer time to relapse relative to oral APs<sup>23,26–30</sup>.

A once-every-three-months paliperidone palmitate (PP3M) formulation was recently approved by the FDA for the treatment of schizophrenia in adult patients adequately treated with PP1M<sup>31</sup> for at least 4 months. The safety and efficacy of PP3M were demonstrated in two double-blind, randomized clinical trials<sup>32,33</sup>. However, there is a need to better understand the characteristics and treatments patterns of patients initiating PP3M in a real-world setting.

To fulfill this gap, this study assessed patient demographic and clinical characteristics of adult patients with schizophrenia initiating PP3M, as well as adherence to mental health-related medications, healthcare resource utilization (HRU), and PP1M treatment patterns prior to PP3M initiation. This study also aims at measuring PP3M treatment patterns, including adherence to and persistence with PP3M treatment.

## Methods

### Data sources

Pharmacy and medical claims from May 2014 to September 2016 for adult patients with schizophrenia initiated on PP3M in the Symphony Health Solutions' (SHS) Patient Transactional Datasets were analyzed. The SHS database is a provider-based, longitudinal patient data source which captures adjudicated prescription claims across the United States and covers all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. SHS links healthcare data for the US population from three basic sources: pharmacy point of service; switch/network transactions; and additional direct prescription (Rx), medical, and hospital claims data. This database reflects pharmacy claims in final (paid) form and submitted medical claims. Patients are linked between the different pharmacy and clinic networks through a unique patient ID created based on patients' demographic characteristics, including first name, last name, date of birth, zip code and gender.

All data collected from the database is de-identified in compliance with the patient confidentiality requirement of the Health Insurance Portability and Accountability Act (HIPAA).

### Study design

A retrospective longitudinal cohort study design was used. The index date was defined as the date of the first final approved claim for PP3M. The baseline period was defined as the 12 months of continuous clinical activity prior to the index date. The observation (follow-up) period for assessment of the utilization and dosing patterns spanned from the index date up until the end of clinical activity (defined as the date of the last medical or drug claim in the database for a

particular patient) or lack of available follow-up data (data cut-off date is 30 September 2016), whichever occurred first.

Two cohorts were investigated: first, the cohort of all patients initiating PP3M (overall PP3M cohort) and second, the cohort of patients initiating PP3M who transitioned from PP1M based on prescribing guidelines and on an adaptation of the strict clinical trial protocol for PP1M to PP3M transition<sup>32</sup> (per label PP3M cohort).

### Patient selection

Patients were included in the overall PP3M cohort if they were at least 18 years old, had at least one final approved pharmacy/medical claim for PP3M (the first being defined as the index date), had at least one claim with a diagnosis for schizophrenia (ICD-9: 295.XX [excluding 295.7], ICD-10: F20.XX, F21) anytime during the study period, and at least 12 months of continuous clinical activity before the index date (baseline period). Patients were included in the per label PP3M cohort if, in addition, they had no gap of >45 days in PP1M coverage 4 months prior to PP3M initiation, had the same dosage strength for the last two PP1M claims prior to PP3M initiation, and had the appropriate dosage conversion between the last PP1M and the first PP3M claims (78 mg–273 mg, 117 mg–410 mg, 156 mg–546 mg, or 234 mg–819 mg), as per prescribing guidelines.

### Study endpoints

For the two cohorts, baseline demographic and clinical characteristics were assessed during the 12 month baseline period and included age, gender, US region, insurance plan, number of unique mental health diagnoses, use of mental health-related medications, and the Charlson comorbidity index (CCI).

PP1M treatment patterns before transitioning to PP3M were also assessed during the 12 month baseline period for both cohorts and included the number of PP1M claims, the length of exposure to PP1M treatment, the number of days between PP1M claims, the assessment of appropriate transition from PP1M to PP3M, the proportion of days covered (PDC) by PP1M, and the dose of the last PP1M and the first PP3M claims. For each quarter of the 12 month baseline period, the PDC by any AP treatment, antidepressants, anxiolytics or mood stabilizers, as well as HRU patterns (i.e. outpatient [OP], inpatient [IP], and emergency room [ER] visits) were evaluated.

PP3M treatment patterns were assessed for both cohorts starting at the index date and included the duration of continuous PP3M therapy (defined as having a gap of no more than 45 days between the end of supply of a PP3M claim and the start of a new PP3M claim), the number of PP3M claims, the number of days between PP3M claims, dose strength, and the use of mental-health-related medications during exposure to PP3M treatment. Adherence to PP3M therapy was evaluated using PDC and the medication possession ratio (MPR). The PDC was calculated as the number of non-overlapping days of supply over a fixed period of time

(i.e. 6 months) among patients with  $\geq 6$  months of observation period. The MPR was calculated as the number of days of supply over treatment duration (i.e. the period between the first and the last dispensing of the index medication) and was calculated among patients with  $\geq 2$  PP3M claims. Adherence to therapy was defined using a threshold of  $\geq 0.80$  for PDC and MPR. Persistence was evaluated as the proportion of patients with a second or third dose, among those with sufficient observation period ( $\geq 4$  months after the previous dose).

### Statistical analysis

Descriptive statistics were used to report demographic and clinical characteristics and PP1M treatment patterns at baseline as well as PP3M treatment patterns during the observation period. Means, standard deviations (SDs), and medians were used to describe continuous variables; frequencies and percentages were reported for categorical variables.

All statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

## Results

### Baseline characteristics

Among 7160 adult patients with at least one approved PP3M claim, 5362 (74.9%) had continuous clinical activity for at least 12 months prior to the index date and 1545 (21.6%) also had at least one schizophrenia diagnosis anytime during the study period (Figure 1). Among these 1545 patients (overall PP3M cohort), 1063 (68.8%) transitioned from PP1M to PP3M as per prescribing guidelines and PP3M clinical trial (per label PP3M cohort).

Baseline characteristics are presented in Table 1. In both cohorts, most patients were under 35 years of age (overall PP3M cohort: 33.8%; per label PP3M cohort: 34.1%), were male (overall PP3M cohort: 64.7%; per label PP3M cohort: 66.1%), were from the south region of the US (overall PP3M

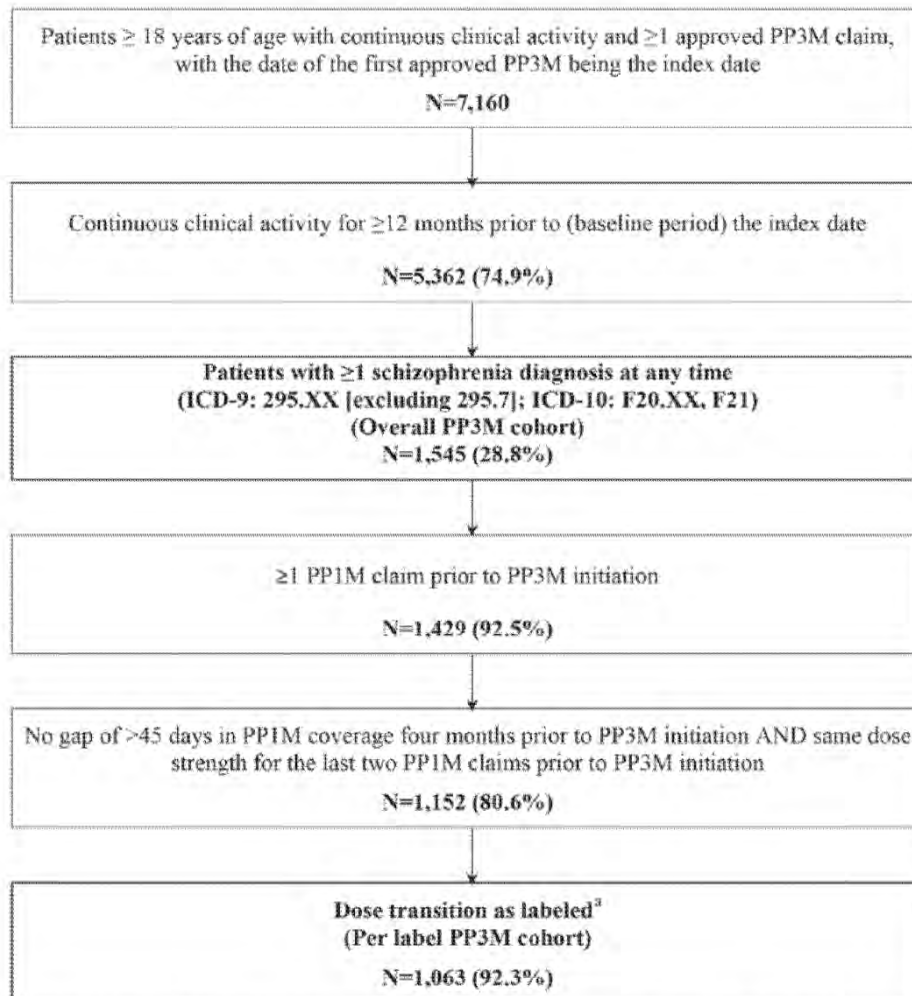


Figure 1. Identification of the study population. Abbreviations. PP1M, once every month paliperidone palmitate; PP3M, once every three months paliperidone palmitate. <sup>a</sup>Correspondence between the dose strength (mg) of the last PP1M claim and the first PP3M claim: 78 mg 273 mg, 117 mg 410 mg, 156 mg 546 mg or 234 mg 819 mg.



Table 1. Demographic and clinical characteristics evaluated during the 12 month baseline period.

Characteristics	Overall PP3M cohort (N 1545)	Per label PP3M cohort (N 1063)
Age categories, n (%)		
18-34	522 (33.8)	363 (34.1)
35-44	359 (23.2)	243 (22.9)
45-54	325 (21.0)	224 (21.1)
≥55	339 (21.9)	233 (21.9)
Gender, n (%)		
Male	1000 (64.7)	703 (66.1)
Female	545 (35.3)	360 (33.9)
US region, n (%)		
South	709 (45.9)	503 (47.3)
Midwest	280 (18.1)	191 (18.0)
West	223 (14.4)	145 (13.6)
Northeast	131 (8.5)	92 (8.7)
Unknown	202 (13.1)	132 (12.4)
Primary insurance plan at index date, n (%)		
Medicare	736 (47.6)	506 (47.6)
Medicaid	640 (41.4)	448 (42.1)
Commercial	163 (10.6)	104 (9.8)
Other	6 (0.4)	5 (0.5)
Quan CCI, mean ± SD [median]	0.6 ± 1.2 [0.0]	0.6 ± 1.2 [0.0]
Number of unique mental health diagnoses, mean ± SD [median]	2.8 ± 3.1 [2.0]	2.7 ± 3.1 [2.0]
Baseline mental health related medication use, n (%)		
APs	1511 (97.8)	1063 (100.0)
Oral typical	231 (15.0)	159 (15.0)
Oral atypical	868 (56.2)	583 (54.8)
Typical LAI	70 (4.5)	54 (5.1)
Atypical LAI	1438 (93.1)	1063 (100.0)
Paliperidone palmitate (PP1M)	1429 (92.5)	1063 (100.0)
Polypharmacy	480 (31.1)	391 (36.8)
Antidepressant	823 (53.3)	558 (52.5)
Anxiolytics	461 (29.8)	310 (29.2)
Mood stabilizer	594 (38.4)	388 (36.5)

Abbreviations. AP, antipsychotic; CCI, Charlson comorbidity index; LAI, long acting injectable therapy; PP1M, once every month paliperidone palmitate; PP3M, once every three months paliperidone palmitate; SD, standard deviation.

cohort: 45.9%; per label PP3M cohort: 47.3%), and had Medicare (47.6% in both cohorts) or Medicaid (overall PP3M cohort: 41.4%; per label PP3M cohort: 42.1%) coverage at the index date. The mean CCI was 0.6 (SD = 1.2) in both cohorts and the mean number of unique mental health diagnoses was 2.8 and 2.7 in the overall PP3M cohort and in the per label PP3M cohort, respectively (SD = 3.1 in both cohorts).

#### PP1M treatment patterns before transitioning to PP3M

Among the 1545 patients in the overall PP3M cohort, 1429 (92.5%) had at least one PP1M claim before transitioning to PP3M. The overall PP3M cohort received on average 8.9 (SD = 3.8) PP1M claims with 33.7 (SD = 17.5) days between consecutive PP1M claims and were exposed to PP1M treatment for 284.9 (SD = 93.9) days, while the subset of patients in the per label PP3M cohort received 9.8 (SD = 3.3) PP1M claims with 31.5 (SD = 7.6) days between consecutive claims and were exposed to PP1M treatment for 302.1 (SD = 90.7) days (Table 2).

Among the overall PP3M cohort, 87.2% had the same dose strength for the last two PP1M claims prior to PP3M initiation, 83.9% had a correspondence between the dose strength of the last PP1M claim and the first PP3M claim as recommended and 75.9% had no gap >45 days in PP1M coverage 4 months prior to PP3M initiation (Table 2). Therefore, the main reason for not transitioning from PP1M to PP3M adequately was the criteria of no gap >45 days in PP1M coverage 4 months prior to PP3M initiation.

The most prevalent dosage for the last PP1M claim was 234 mg for both cohorts (overall PP3M cohort with prior PP1M use: 53.8%; per label PP3M cohort: 56.0%), followed by

Table 2. PP1M treatment patterns during the 12 month baseline period (before transitioning to PP3M).

	Overall PP3M cohort (N 1545)	Per label PP3M cohort (N 1063)
Patients with PP1M use in the baseline period, n (%)	1429 (92.5)	1063 (100.0)
Number of patients transitioning from PP1M to PP3M as per label recommendations <sup>a</sup> , n (%)	1063 (68.8)	1063 (100.0)
No gap of >45 days in PP1M coverage 4 months prior to PP3M initiation	1173 (75.9)	1063 (100.0)
Same dose strength for the last two PP1M claims prior to PP3M initiation	1347 (87.2)	1063 (100.0)
Recommended transition between PP1M and PP3M dosages	1297 (83.9)	1063 (100.0)
Among patients with prior PP1M use	N 1429	N 1063
Number of PP1M claims <sup>b</sup> , mean ± SD [median]	8.9 ± 3.8 [10.0]	9.8 ± 3.3 [11.0]
Baseline exposure to PP1M (days), mean ± SD [median]	284.9 ± 93.9 [338.0]	302.1 ± 90.7 [364.0]
Number of days between two consecutive PP1M dispensings, mean ± SD [median]	33.7 ± 17.5 [30.1]	31.5 ± 7.6 [29.9]
Proportion of days covered (PDC) <sup>b</sup> , n (%)		
PDC < 0.80	900 (63.0)	541 (50.9)
PDC ≥ 0.80	529 (37.0)	522 (49.1)
Dose strength (mg) of the last PP1M claim before transitioning to PP3M, n (%)		
39 mg	0 (0.0)	0 (0.0)
78 mg	19 (1.3)	11 (1.0)
117 mg	192 (13.4)	136 (12.8)
156 mg	449 (31.4)	321 (30.2)
234 mg	769 (53.8)	595 (56.0)
Correspondence between the dose strength (mg) of the last PP1M claim and the first PP3M claim, n (%)		
Recommended transitions	1297 (90.8)	1063 (100.0)
78 mg 273 mg	13 (0.9)	11 (1.0)
117 mg 410 mg	162 (11.3)	136 (12.8)
156 mg 546 mg	400 (28.0)	321 (30.2)
234 mg 819 mg	722 (50.5)	595 (56.0)
Non recommended transitions	132 (9.2)	

Abbreviations. PP1M, once every month paliperidone palmitate; PP3M, once every three months paliperidone palmitate; SD, standard deviation.

<sup>a</sup>Defined as having no gap of >45 days in PP1M coverage 4 months prior to PP3M initiation, having the same dosage strength for the last two PP1M claims prior to PP3M initiation, and an appropriate dosage conversion between the last PP1M and the first PP3M claims (78 mg 273 mg, 117 mg 410 mg, 156 mg 546 mg, or 234 mg 819 mg).

<sup>b</sup>Evaluated during the baseline period.



156 mg (overall PP3M cohort with prior PP1M use: 31.4%; per label PP3M cohort: 30.2%), 117 mg (overall PP3M cohort with prior PP1M use: 13.4%; per label PP3M cohort: 12.8%), and 78 mg (overall PP3M cohort with prior PP1M use: 1.3%; per label PP3M cohort: 1.0%; Table 2).

Adherence to PP1M prior to PP3M initiation (12 month baseline period) was seen to be higher for patients in the per label PP3M cohort compared to patients in the overall PP3M cohort with prior PP1M use (proportion of patients with a PDC by PP1M  $\geq 0.80$ : 49.1% vs. 37.0%; Table 2).

#### Baseline adherence to mental-health-related medication by quarter

In baseline quarters closer to PP3M initiation, the proportion of patients in the overall PP3M cohort with a PDC by any AP  $\geq 80\%$  increased from 66.7% at the fourth quarter to 74.2% at the first quarter prior to PP3M initiation. Furthermore, among the subset of patients in the per label PP3M cohort, the proportion achieving PDC by any AP  $\geq 80\%$  was generally higher at each quarter relative to the overall PP3M cohort and increased from 71.3% to 82.3% (Figure 2).

Similarly, in baseline quarters closer to PP3M initiation, the proportion of patients in the overall PP3M cohort with a PDC by antidepressants  $\geq 80\%$ , a PDC by anxiolytics  $\geq 80\%$ , and a PDC by mood stabilizers  $\geq 80\%$  increased from 54.6% to 64.0%, from 41.0% to 50.2%, and from 54.7% to 64.9%, respectively. The proportion of patients with a PDC  $\geq 0.80$  was consistently higher at each quarter and the same trend was observed in the per label PP3M cohort (Figure 2).

#### Baseline healthcare resource utilization patterns by quarter

There was a decrease in the proportion of patients with  $\geq 1$  ER visit in baseline quarters closer to PP3M initiation in the overall PP3M cohort (from 14.7% at the fourth quarter to 11.1% at the first quarter prior to PP3M initiation) and in the per label PP3M cohort (from 13.4% to 9.2%). A decreasing trend was also observed in the proportion of patients with  $\geq 1$  IP visit (from 6.6% to 3.2% in the overall PP3M cohort and from 6.5% to 2.5% in the per label PP3M cohort) as well as in the proportion of patients with  $\geq 1$  OP visit (from 50.9% to 48.1% in the overall PP3M cohort and from 48.9% to 47.5% in the per label PP3M cohort; Figure 3).

Similarly, in baseline quarters closer to PP3M initiation, a decrease in the mean number of monthly ER visits (from 0.09 at the fourth quarter to 0.07 at the first quarter prior to PP3M initiation in the overall PP3M cohort and from 0.08 to 0.06 in the per label PP3M cohort) and monthly IP visits (from 0.03 to 0.02 in the overall PP3M cohort and from 0.03 to 0.01 in the per label PP3M cohort) was observed. A decreasing trend was also observed in the mean number of OP visits per month (from 0.74 to 0.68 in the overall PP3M cohort and from 0.73 to 0.69 in the per label PP3M cohort; Figure 4).

#### PP3M treatment patterns

There was on average 26.9 (SD = 13.9) days between the last PP1M and the first PP3M claims for patients in the per label PP3M cohort. In contrast, there were on average 40.0 days (SD = 45.6) in the overall PP3M cohort (Table 3).

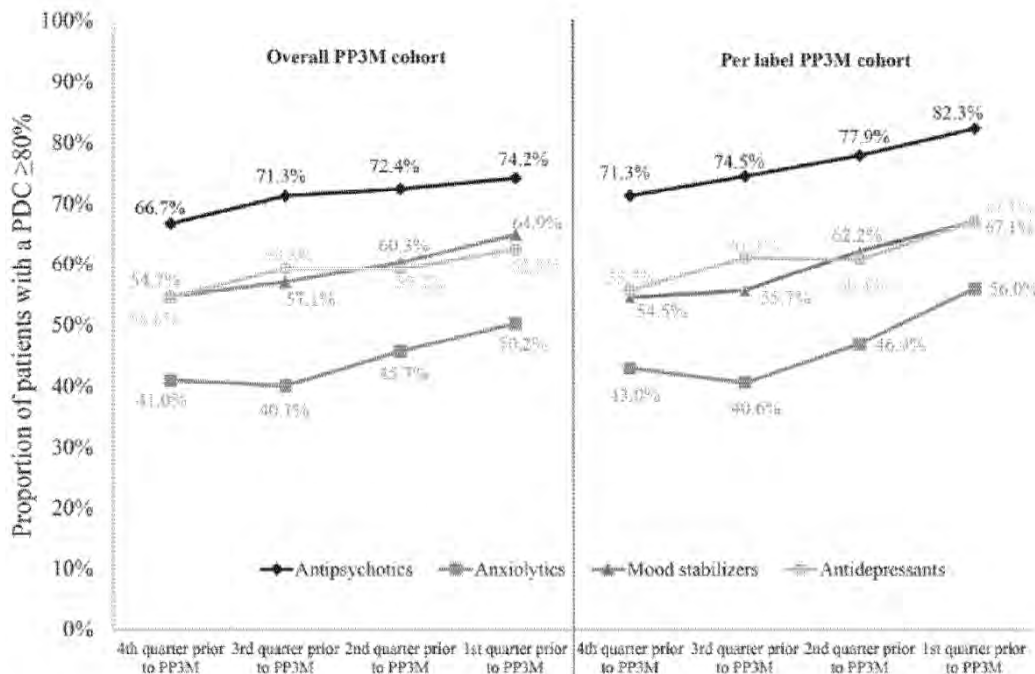


Figure 2. Adherence to antipsychotics and mental health related medication for each quarter of the baseline period.

1768 K. JOSHI ET AL.

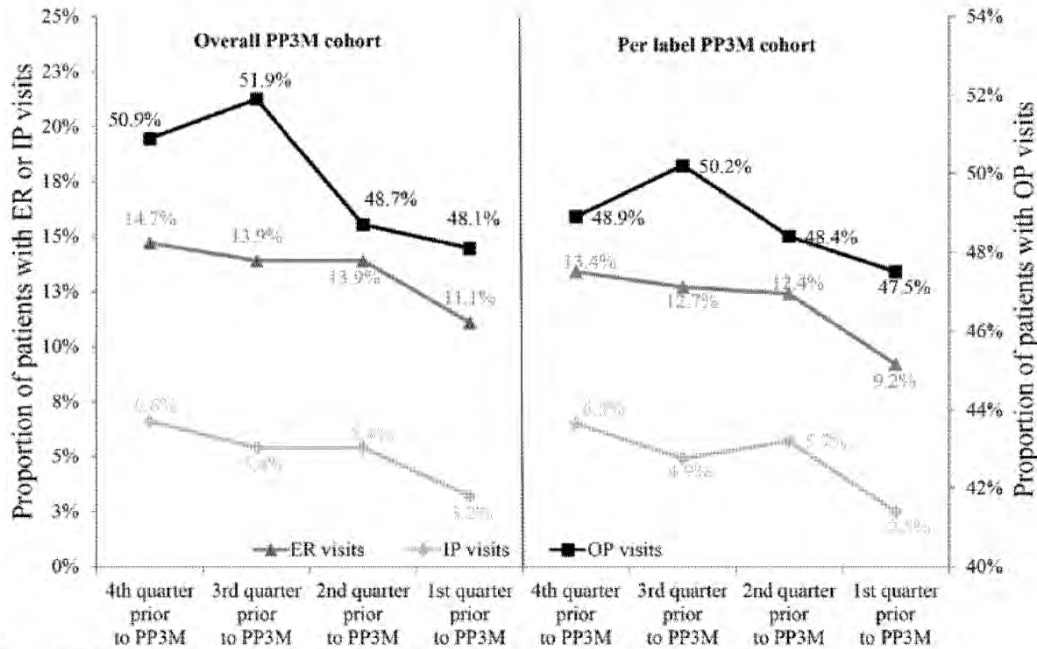


Figure 3. Proportion of patients with ER, IP and OP visits for each quarter of the baseline period.

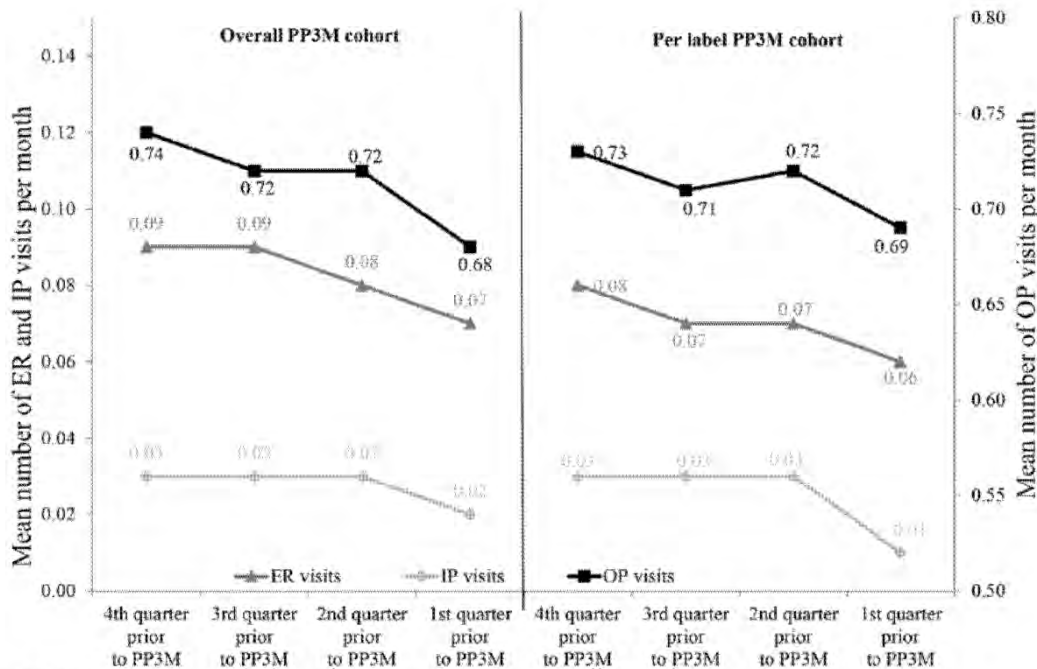


Figure 4. Mean number of ER, IP and OP visits per month for each quarter of the baseline period.

The most commonly used first PP3M dose was 819 mg (overall PP3M cohort: 52.7%; per label PP3M cohort: 56.0%) followed by 546 mg (overall PP3M cohort: 31.7%; per label PP3M cohort: 30.2%), 410 mg (overall PP3M cohort: 13.2%; per label PP3M cohort: 12.8%), and 273 mg (overall PP3M cohort: 2.5%; per label PP3M cohort: 1.0%; Table 3).

Among patients in the overall PP3M cohort with  $\geq 2$  PP3M claims ( $N=1066$ ), the mean MPR was 0.97 (SD=0.08) and 95.6% of the patients had an MPR  $\geq 0.8$ . Similarly, among those in the per label PP3M cohort with  $\geq 2$  PP3M claims ( $N=767$ ), the mean MPR was 0.97 (SD=0.08) and 96.6% had an MPR  $\geq 0.8$  (Table 3). The proportion of patients with a

Table 3. PP3M treatment patterns.

	Overall PP3M cohort (N 1545)	Per label PP3M cohort (N 1063)
Duration of continuous PP3M therapy <sup>a</sup> , days, mean ± SD [median]	177.3 ± 109.9 [162.0]	186.5 ± 112.8 [174.0]
Number of PP3M claims, mean ± SD [median]	2.5 ± 1.4 [2.0]	2.6 ± 1.4 [2.0]
Distribution of the number of PP3M claims, n (%)		
1	479 (31.0)	296 (27.8)
2	376 (24.3)	247 (23.2)
3 or more	690 (44.7)	520 (48.9)
Dosing patterns		
First dose		
Patients with a first dose, n (%)	1545 (100.0)	1063 (100.0)
Days since last PP1M dose, mean ± SD [median]	40.0 ± 45.6 [28.0]	26.9 ± 13.9 [28.0]
Dose strength (mg), n (%)		
273	38 (2.5)	11 (1.0)
410	204 (13.2)	136 (12.8)
546	489 (31.7)	321 (30.2)
819	814 (52.7)	595 (56.0)
Second dose		
Patients with >4 months of follow up after first dose, n (%)	1136 (73.5)	794 (74.7)
Patients with a second dose, n (%)	968 (85.2)	698 (87.9)
Days since last PP3M dose, mean ± SD [median]	89.2 ± 29.7 [88.0]	89.8 ± 29.1 [88.0]
≥120 days, n (%)	58 (6.0)	36 (5.2)
Dose strength (mg), n (%)		
273	15 (1.5)	5 (0.7)
410	134 (13.8)	91 (13.0)
546	308 (31.8)	215 (30.8)
819	511 (52.8)	387 (55.4)
Change from first dose to second dose, n (%)		
Increase	17 (1.8)	7 (1.0)
Same dose	945 (97.6)	686 (98.3)
Decrease	6 (0.6)	5 (0.7)
Third dose		
Patients with >4 months of follow up after second dose, n (%)	695 (45.0)	513 (48.3)
Patients with a third dose, n (%)	607 (87.3)	459 (89.5)
Days since last PP3M dose, mean ± SD [median]	86.5 ± 22.3 [85.0]	86.6 ± 21.4 [85.0]
≥120 days, n (%)	28 (4.6)	19 (4.1)
Dose strength (mg), n (%)		
273	7 (1.2)	3 (0.7)
410	79 (13.0)	54 (11.8)
546	200 (32.9)	149 (32.5)
819	321 (52.9)	253 (55.1)
Change from second dose to third dose, n (%)		
Increase	15 (2.5)	11 (2.4)
Same dose	585 (96.4)	443 (96.5)
Decrease	7 (1.2)	5 (1.1)
Days between subsequent doses <sup>b</sup> , mean ± SD [median]	87.4 ± 19.6 [86.0]	87.0 ± 18.5 [86.0]
Adherence to PP3M		
MPR <sup>c</sup> , mean ± SD [median]	0.97 ± 0.08 [1.00]	0.97 ± 0.08 [1.00]
MPR <sup>c</sup> ≥ 0.80, n (%)	1019 (95.6)	741 (96.6)
PDC <sup>d</sup> at 6 months, n (%)	907 (58.7)	651 (61.2)
PDC, mean ± SD [median]	0.89 ± 0.18 [0.98]	0.90 ± 0.17 [0.98]
PDC ≥ 0.80, n (%)	741 (81.7)	549 (84.3)

Abbreviations. PDC, proportion of days covered; PP1M, once every month paliperidone palmitate; PP3M, once every three months paliperidone palmitate; MPR, medication possession ratio; SD, standard deviation.

<sup>a</sup>Continuous PP3M therapy was defined as having a gap of no more than 45 days between the end of supply of a PP3M claim and the start of a new PP3M claim, starting from the index date.

<sup>b</sup>Among patients with more than three PP3M claims and at least 4 months of follow up between claims.

<sup>c</sup>MPR was calculated among patients with at least two claims of PP3M. A MPR higher than 1 was truncated to 1.

<sup>d</sup>PDC was calculated as the sum of the number of unique days during which the patient had PP3M, divided by a fixed time interval.

PDC ≥ 0.8 at 6 months was 81.7% in the overall PP3M cohort and 84.3% in the per label PP3M cohort (Table 3).

Almost three-quarters of the patients had ≥ 4 months of follow-up after the first dose in both cohorts, of which 85.2% of the overall PP3M cohort (87.9% of the per label PP3M cohort) had a second dose (Table 3). The strength of this second dose was identical to the first one in 97.6% (per label PP3M cohort: 98.3%) of the cases (Table 3). Among patients with <4 months of follow up after the first dose in the per label PP3M cohort (N=269), 69 patients (25.7%) still had a second dose and 160 patients (59.5%) received their index injection within the last 3 months before the data cutoff

date (June–September 2016) and no second dose (data not shown). Only 40 (14.9%) patients received their index PP3M prior to June 2016 and did not have a second dose.

Similarly, among the 45.0% (per label PP3M cohort: 48.3%) of patients with ≥ 4 months of follow-up after the second dose, 87.3% (per label PP3M cohort: 89.5%) of them had a third dose in both cohorts. The third dose had the same strength as the second dose for 96.4% (per label PP3M cohort: 96.5%) of the patients (Table 3). Among patients with <4 months of follow up after the second dose in the per label PP3M cohort (N=185 patients), 61 patients (33.0%) still had a third dose and 100 patients (54.1%) received their index

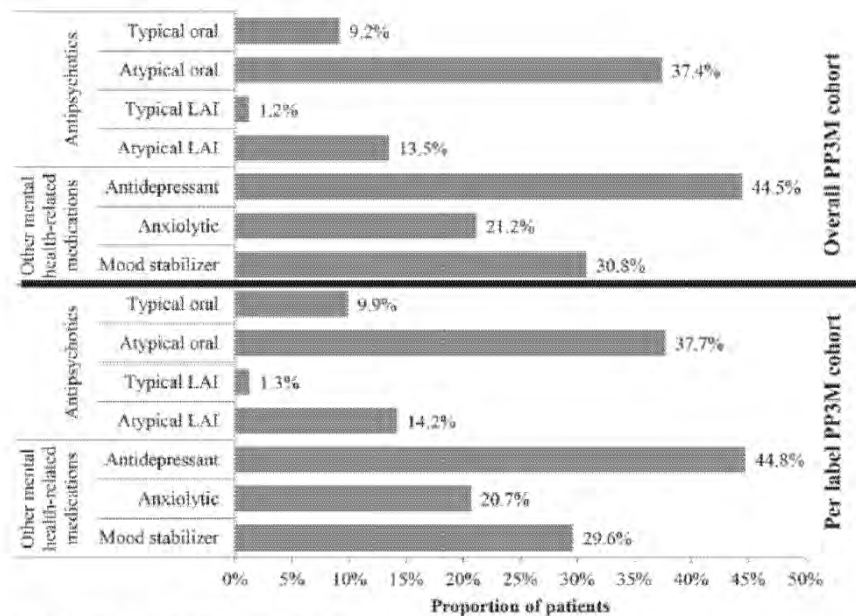


Figure 5. Mental health related medication use during exposure to PP3M.

injection within the last 6 months before the data cutoff date (March–September 2016) and no third dose. Only 24 (13.0%) patients received their index PP3M prior to March 2016 and did not have a third dose.

Finally, 42.6% (per label PP3M cohort: 45.2%) of the patients had  $\geq 8$  months of follow-up after the first dose, of whom 75.1% (per label PP3M cohort: 79.0%) had a third dose in the overall PP3M cohort and the per label PP3M cohort, respectively (data not shown). The third dose had the same strength as the first dose for 95.5% (per label PP3M cohort: 96.1%) of the patients.

During exposure to PP3M treatment, the most commonly used mental-health-related medications were antidepressants (overall PP3M cohort: 44.5%; per label PP3M cohort: 44.8%), atypical oral APs (overall PP3M cohort: 37.4%; per label PP3M cohort: 37.7%), mood stabilizers (overall PP3M cohort: 30.8%; per label PP3M cohort: 29.6%), and anxiolytics (overall PP3M cohort: 21.2%; per label PP3M cohort: 20.7%; Figure 5).

## Discussion

This retrospective observational study found that PP3M was generally administered to schizophrenia patients following the prescribing guidelines. The most common first PP3M dose strength was 819 mg (the highest dosage available) and most patients had a consistent dose for their first three PP3M claims. The average number of days between subsequent PP3M claims was also consistent with the recommendations. In the overall PP3M cohort, as well as the per label PP3M cohort, patients demonstrated stabilization observed through improvement in adherence and reduction in health-care resource utilization by quarters leading up to PP3M initiation. Finally, a high proportion of patients were persistent with and adherent to their PP3M treatment, with more than

80% of the population having a PDC at 6 months  $\geq 0.80$  and most of the patients having subsequent PP3M claims within 4 months of interval.

The vast majority of patients (68.8%) transitioned from PP1M to PP3M based on the prescribing guidelines and on an adaptation of the strict clinical trial protocol for PP1M to PP3M transition<sup>32</sup>. The main reason for not transitioning as recommended was the presence of gaps  $>45$  days in PP1M coverage 4 months prior to PP3M initiation, which was used to define patients being “adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least four months” from the prescribing guidelines<sup>31</sup>. This algorithm has been developed to mimic the PP3M clinical trial protocol in which patients received PP1M for 120 days at the following schedule: day 1, 8, 36, 64, and 92. However, treating healthcare providers may have clinical reasons for not conforming with the guidelines in certain circumstances where individualized patient care is required. For example, a psychiatrist may consider a patient to be adequately treated with PP1M for at least 4 months to be transitioned to PP3M while gaps of more than 45 days occurred during the PP1M coverage. Hence, observed findings may differ from the prescribing guidelines in the real-world practice of psychiatry. It is also possible that some of the initial claims for PP1M were not captured in the data (e.g. samples). However, it is important to note that there were no substantial differences in the baseline characteristics or the treatment patterns between the overall PP3M cohort and the per label PP3M cohort.

The proportion of patients receiving a second or third dose was calculated among patients with  $\geq 4$  months of follow-up after their first or second PP3M dose to allow sufficient time to observe this additional dose. The vast majority of the excluded patients either still received an additional dose or did not have  $\geq 4$  months of follow-up because of the



data cutoff date. Only less than 15% of the patients with <4 months of follow-up received their first/second PP3M dose soon enough to potentially have  $\geq 4$  months of follow-up but did not have a subsequent PP3M claim.

To the best of our knowledge this is the first study to assess the transition between PP1M and PP3M in a real-world setting. However, results of the current study are consistent with previous literature with respect to adherence and HRU. Indeed, since lower dosing frequency has already been associated with better adherence<sup>17,18,26,34</sup>, high adherence with 1 and 3 month LAIs was to be expected. In addition, a systematic review found that poor adherence to AP treatment was associated with increased HRU<sup>35</sup>. In this study, a trend was observed with an increased adherence in the baseline quarters prior to PP3M initiation and a decrease in inpatient, outpatient, and emergency-room visits.

A retrospective claims-based study on Medicaid patients after discharge from a schizophrenia-related hospitalization mentioned that 51.0% of the patients had a PDC by PP1M at 6 months higher than 0.80 and 48.2% had a PDC by any LAI at 6 months higher than 0.80<sup>23</sup>. In our study, we found a substantially higher proportion of patients with a PDC by PP3M at 6 months higher than 0.80 (59% and 61.9% depending on the cohort). These results are therefore in line with the hypothesis that a lower dose frequency may increase adherence to AP medication. Higher adherence, along with longer half-life, may be associated with better outcomes, including time to relapse<sup>36</sup>.

Further research could also consider cost analyses. Some studies have already shown that PP1M results in lower medical costs when compared to oral APs<sup>34,37-39</sup>. The drug cost of PP3M is in parity to PP1M. However, it is expected that PP3M utilization will incur reduced costs related to drug administration compared to PP1M due to decreased dosing frequency.

This study was subject to some limitations. First, SHS is a provider-based data source and a unique patient ID is created based on patients' first name, last name, date of birth, zip code and gender to link the information collected from the different pharmacy and clinic networks. The database will not capture the services patients received from a provider that is outside of the SHS network. This explains why a high proportion of patients were removed in the selection process because they did not have at least one schizophrenia diagnosis (Figure 1). This does not mean that the excluded patients did not have schizophrenia, but that the diagnosis may not have been captured in the Symphony database. Also, based on previous analyses using SHS database, even if patients may change providers for obtaining their different medications, they tend to obtain the same medication through the same provider, therefore enabling us to analyze treatment patterns of a specific medication. Second, as with all real-world data sources, this data were subject to billing inaccuracies and missing data. Third, adherence measures such as PDC or MPR do not account for whether the drugs dispensed were actually taken as prescribed. This may overestimate patient adherence, especially for oral medication, for which we assumed that patients take their medication as prescribed (e.g. one pill per day), whereas for LAI, the duration of effect

for one injection is independent of any further action by the patient. Finally, we could not assess any trend on health-care resource utilization and associated costs after PP3M initiation given the limited sample with sufficient follow-up after index date.

Despite these limitations, SHS is a robust source of data which captures a high proportion of the prescription transactions in the US and provides access to recent information (up to September 2016). The SHS database thus offers the advantage of broad and timely access to data on the utilization of new drugs and provides a much larger sample size of PP3M users compared to other available claims or Electronic Medical Records (EMR) databases.

## Conclusions

Patients initiated on PP3M demonstrated decreased HRU and increased adherence in quarters closer to PP3M initiation. The results also suggest optimal adherence and persistency with PP3M, the only 3 month antipsychotic therapy option for patients suffering with schizophrenia. Further research with longer follow-up is needed to confirm findings on PP3M treatment patterns and adherence.

## Transparency

### Declaration of funding

This research was funded by Janssen Scientific Affairs LLC.

### Declaration of financial/other relationships

K.J., B.B. and N.T. have disclosed that they are employees of Janssen Scientific Affairs LLC and Johnson & Johnson. M. H.L., W.W., B.E. and P.L. have disclosed that they are employees of Analysis Group Inc., a consulting company that has received research funds from Janssen Scientific Affairs LLC.

CMRO peer reviewers on this manuscript have received an honorarium from CMRO for their review work, but have no relevant financial or other relationships to disclose.

Janssen Scientific Affairs, LLC

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**APPX14094 - APPX14196**

**CONTAIN MATERIALS SUBJECT TO  
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**Appx14094 - Appx14196**  
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Dawn H. Wilson  
(Name)

/Dawn H. Wilson/  
(Signature)

February 20, 2018  
(Date of Signature)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants : Gopal, *et al.* Docket No.: JPI5001USNP  
Serial No. : 15/090,889 Art Unit: 1621  
Filed : April 5, 2016 Examiner: BAEK, BONG-SOOK  
Title : Dosing Regimen For Missed Doses for Long-Acting Injectable  
Paliperidone Esters

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**RESPONSE TO NON-FINAL OFFICE ACTION**

Dear Sir:

In response to the Non-Final Office Action having a Notification date of November 20, 2017 ("Office Action:"), applicants submit the following remarks. No fee is believed to be due for this submission.

**Amendments to the Claims** begin on page 2 of this paper

**Remarks** begin on page 8 of this paper.

EXPERTS\_MYL\_002135

Appx14445



Application Number: 15/090,889  
Docket No.: JPI5001USNP

**Amendments to the Claims:**

The listing of the claims will replace all previous versions, and listings, of the claims.

1. (Currently Amended) A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with a 3-month injectable paliperidone palmitate depot (PP3M), wherein said patient had been last administered a PP3M injection more than 9 months ago, misses for a period of nine months or longer the next scheduled maintenance dose of the PP3M should be administered 3-month injectable paliperidone palmitate depot, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of 150 mg eq. of ~~the~~ monthly injectable paliperidone palmitate depot (PP1M);
- (2) administering intramuscularly in the deltoid muscle of said patient a second reinitiation loading dose of 100 mg eq. of PP1M ~~the monthly injectable paliperidone palmitate depot~~ on about the 4th day to about the 12th day after administering ~~of~~ said first reinitiation loading dose;
- (3) administering intramuscularly in the deltoid or gluteal muscle of said patient a first reinitiation maintenance dose of 50 mg eq. to about 150 mg eq. of PP1M ~~the monthly injectable paliperidone palmitate depot~~ on about the 23th day to about the 37th ~~rd~~ day after administering ~~of~~ said second reinitiation loading dose;
- (4) administering intramuscularly in the deltoid or gluteal muscle of said patient a second reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M ~~monthly injectable paliperidone palmitate depot~~ on about the 23rd day to about the 37th day after administering ~~of~~ the first reinitiation maintenance ~~additional~~ dose;
- (5) administering intramuscularly in the deltoid or gluteal muscle of said patient a third reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq.

Application Number: 15/090,889  
Docket No.: JPI5001USNP

of PP1M ~~monthly injectable paliperidone palmitate depot~~ on about the 23rd day to about the 37th day after administering of the second reinitiation maintenance dose; and

- (6) administering intramuscularly in the deltoid or gluteal muscle of said patient from about 175 mg eq. to about 525 mg eq. of PP3M ~~the 3-month formulation of paliperidone palmitate~~ on about the 23rd day to about the 37th day after administering of the ~~third~~ a last reinitiation maintenance dose of monthly injectable paliperidone palmitate.

2. (Original) The method of claim 1, wherein said patient is in need of treatment for psychosis.

3. (Original) The method of claim 2, wherein said patient is in need of treatment for schizophrenia.

4. (Original) The method of claim 2, wherein said patient is in need of treatment for bipolar disorder.

5. (Currently Amended) A dosing regimen for administering an injectable paliperidone palmitate depot to a patient in need of psychiatric treatment that has been treated with PP3M ~~a 3-month injectable paliperidone palmitate depot~~, wherein said patient had been last administered a PP3M injection 4 to 9 months ago ~~misses for a period of more than or equal to four months and up to nine months~~ the next scheduled maintenance dose of PP3M ~~should be administered~~ the 3-month injectable paliperidone palmitate depot, comprising:

- (1) administering intramuscularly in the deltoid muscle of said patient a first reinitiation loading dose of PP1M ~~the monthly injectable paliperidone palmitate depot~~;
- (2) administering intramuscularly in the deltoid ~~or gluteal~~ muscle of said patient a second reinitiation loading dose of PP1M ~~the monthly injectable paliperidone~~

Application Number: 15/090,889  
Docket No.: JPI5001USNP

~~palmitate depot~~ on about the 4th day to about the 12th day after administering of said first reinitiation loading dose; and

- (3) ~~administer~~ administering intramuscularly in the deltoid or gluteal muscle of said patient ~~the a~~ a reinitiation dose of PP3M 3-month formulation of paliperidone palmitate ~~in the range of about 175mg eq. to about 525 mg eq.~~ on about the 23rd day to about the 37th day after administering the second reinitiation loading dose of PP1M ~~monthly injectable paliperidone palmitate~~ wherein said first and second reinitiation loading ~~dose~~ doses and the reinitiation PP3M 3-month formulation of paliperidone palmitate dose are selected from the table below based on the amount of the missed dose

<b>Missed Dose</b>	<b><del>Administer PP1M, two doses one week apart (into deltoid muscle)</del></b>		<b>Then administer PP3M (into deltoid<sup>a</sup> or gluteal muscle)</b>
	<b><del>Day 1</del></b>	<b><del>Day 8</del></b>	<b><del>1 month after day 8</del></b>
175 mg eq.	50 mg eq. →	50 mg eq. →	175 mg eq.
263 mg eq.	75 mg eq. →	75 mg eq. →	263 mg eq.
350 mg eq.	100 mg eq. →	100 mg eq. →	350 mg eq.
525 mg eq.	100 mg eq. →	100 mg eq. →	525 mg eq.

<u>Missed Dose of PP3M</u>	<u>Reinitiation Doses of PP1M</u>	<u>Reinitiation Dose of PP3M</u>
<u>175 mg eq.</u>	<u>50 mg eq.</u>	<u>175 mg eq.</u>
<u>263 mg eq.</u>	<u>75 mg eq.</u>	<u>263 mg eq.</u>
<u>350 mg eq.</u>	<u>100 mg eq.</u>	<u>350 mg eq.</u>
<u>525 mg eq.</u>	<u>100 mg eq.</u>	<u>525 mg eq.</u>

6. (Original) The method of claim 5, wherein said patient is in need of treatment for psychosis.

7. (Original) The method of claim 5, wherein said patient is in need of treatment for schizophrenia.

Application Number: 15/090,889  
Docket No.: JPI5001USNP

8. (Original) The method of claim 5, wherein said patient is in need of treatment for bipolar disorder.
9. (New) The method of claim 5 wherein the second reinitiation dose of PP1M is administered about 7 days after administering said first reinitiation loading dose of PP1M.
10. (New) The method of claim 9 wherein the second reinitiation dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.
11. (New) The method of claim 5 wherein the reinitiation dose of PP3M is administered about 30 days after administering said second reinitiation loading dose of PP1M.
12. (New) The method of claim 11 wherein the reinitiation dose of PP3M is administered 30 days after administering said second reinitiation loading dose of PP1M.
13. (New) The method of claim 5 wherein the reinitiation dose of PP3M is administered about a month after administering said second reinitiation loading dose of PP1M.
14. (New) The method of claim 11 wherein the reinitiation dose of PP3M is administered a month after administering said second reinitiation loading dose of PP1M.
15. (New) The method of claim 1 wherein the second reinitiation loading dose of PP1M is administered about 7 days after administering said first reinitiation loading dose of PP1M.
16. (New) The method of claim 9 wherein the second reinitiation loading dose of PP1M is administered 7 days after administering said first reinitiation loading dose of PP1M.

Application Number: 15/090,889  
Docket No.: JPI5001USNP

17. (New) The method of claim 1 wherein the first reinitiation maintenance dose of PP1M is administered about 30 days after administering said second reinitiation loading dose of PP1M.
18. (New) The method of claim 1 wherein the first reinitiation maintenance dose of PP1M is administered 30 days after administering said second reinitiation loading dose of PP1M.
19. (New) The method of claim 1 wherein the second reinitiation maintenance of PP1M is administered about 30 days after administering said first reinitiation maintenance dose of PP1M.
20. (New) The method of claim 1 wherein the second reinitiation maintenance of PP1M is administered 30 days after administering said first reinitiation maintenance dose of PP1M.
21. (New) The method of claim 1 wherein the third reinitiation maintenance of PP1M is administered about 30 days after administering said second reinitiation maintenance dose of PP1M.
22. (New) The method of claim 1 wherein the third reinitiation maintenance of PP1M is administered 30 days after administering said second reinitiation maintenance dose of PP1M.
23. (New) The method of claim 1 wherein PP3M is administered about 30 days after administering said last reinitiation maintenance of PP1M.
24. (New) The method of claim 1 wherein PP3M is administered 30 days after administering said last reinitiation maintenance of PP1M.

Application Number: 15/090,889  
Docket No.: JPI5001USNP

25. (New) The method of claim 1 wherein PP3M is administered about a month after administering said last reinitiation maintenance of PP1M.

26. (New) The method of claim 1 wherein PP3M is administered a month after administering said last reinitiation maintenance of PP1M.

27. (New) The method of claim 1 further comprising administering intramuscularly in the deltoid or gluteal muscle of said patient a fourth reinitiation maintenance dose of from about 50 mg eq. to about 150 mg eq. of PP1M on about the 23rd day to about the 37th day after administering the third reinitiation maintenance dose.

28. (New) The method of claim 27 wherein said fourth reinitiation maintenance of PP1M is administered about 30 days after administering said third reinitiation maintenance dose of PP1M.

29. (New) The method of claim 28 wherein said fourth reinitiation maintenance of PP1M is administered 30 days after administering said third reinitiation maintenance dose of PP1M.

Application Number: 15/090,889  
Docket No.: JPI5001USNP

**REMARKS**

Claims 1-29 are pending in the application.

New claims 9-29 have been added. No new matter has been added.

Claims 1 and 5 have been amended. No new matter has been added.

**Claim Objections**

Claim 5 is objected to for typographical errors. Applicants have corrected the error identified by the Examiner.

Thus, Applicants respectfully request withdrawal of the objection.

**Claim Rejections Under 35 U.S.C. §103**

Claims 1-8 are rejected under 35 U.S.C. §103 as being unpatentable over US2011/0105536 (“536 publication”) in view of Osborne et al., 2012, Health and Quality of Life Outcomes 10:35 (“Osborne”). Applicants respectfully disagree.

The currently pending claims are directed to methods of getting patients back onto a 3-month injectable paliperidone palmitate depot medication (PP3M) when a dose has been missed by a month or more. In that situation, the patient cannot just be given a PP3M injection and continue with the medication. A reinitiation dosing regimen must be administered that includes some administration of 1-month injectable paliperidone palmitate depot medication (PP1M) before getting back onto PP3M.

PP1M and PP3M have the same active agent (paliperidone palmitate) that has been made into nanoparticles. Upon injection in to the body, the nanoparticles dissolve and the active agent is released into circulation. The difference between PP1M and PP3M is the size of the nanoparticles administered. The larger PP3M nanoparticles take longer to fully dissolve thus allowing there to be 3 months between dose administration. The smaller PP1M nanoparticles fully dissolve in one month necessitating monthly administration.



Application Number: 15/090,889  
Docket No.: JPI5001USNP

Patients initially getting onto a long acting injectable paliperidone palmitate must first start by getting onto PP1M. There is a specific initiation dosing regimen needed to have patients get a therapeutic plasma levels of the active agent quickly without oral supplementation. This initiation dosing regimen is disclosed in US Patent No. 9,439,906 (the "906 patent"). It was discovered that administration of PP1M into the deltoids results in a faster rise in the initial plasma concentration, thereby facilitating a rapid attainment of potential therapeutic concentrations. Example 7 of the '906 patent describes the factors which lead to switch from administering gluteal initiation doses (which would be the normal method of administering long acting injectables) to deltoid administration. The modeling described in Example 7 of the '906 patent points to the desirability of day 1, 150mg eq. followed by day 8, 100 mg. eq. doses for initiation of treatment to achieve a therapeutic level of paliperidone faster in patients receiving treatment. These factors were identified after a failed Phase III clinical study with a more conventional dosing regimen. A large amount of money and effort was invested to conduct the initial Phase III trial. Such investments would not have been made if it was obvious that the more conventional dosing would fail.

For a patient to get onto PP3M, there is no equivalent initiation dosing. A patient must first be treated and stable on PP1M for at least 4 months. A PP3M injection is then given at the time that the patient would have received their next PP1M injection. Subsequent injections of PP3M are then administered every 3 months  $\pm$  2 weeks. If a maintenance dose of PP3M is missed, there are different methods disclosed in the instant application for how to get a patient back onto PP3M safely.

Pending claims 5-14 describe the methods to be used to get a patient back onto PP3M if the last dose of PP3M administered to the patient was given 4-9 months ago. Pending claims 1-4 and 15-29 describe the methods to be used to get a patient back onto PP3M if the last dose of PP3M administered to the patient was given more than 9 months ago. Both methods include giving two reinitiation doses of PP1M. For patients that have last been administered PP3M more than 9 months ago, they must also receive at least 3 reinitiation maintenance doses of PP1M before getting back onto PP3M.

Application Number: 15/090,889  
Docket No.: JPI5001USNP

The '536 publication a dosing regimen for a patient to get back onto PP1M after a missed dose of PP1M. This regimen includes either (1) one reinitiation loading dose of PP1M and one reinitiation maintenance dose of PP1M before continuing with monthly injections of PP1M or (2) two reinitiation loading doses of PP1M and one reinitiation maintenance dose of PP1M before continuing with monthly injections of PP1M. This is different than either methods described in the present application. Neither of the presently claimed methods use just one reinitiation loading dose of PP1M or just one reinitiation maintenance dose of PP1M. In fact, the methods in claims 5-14 do not include any reinitiation maintenance doses of PP1M.

One skilled in the art would not have any understanding of how to get a patient back onto PP3M from the disclosure of the '536 publication. The inventors of the instant application had to distinguish the different patient populations (i.e., those that had a PP3M dose 4-9 months ago vs those that had a PP3M dose more than 9 months ago) and how to treat them differently. The exact number of reinitiation loading doses and their amounts could not be learned from the '536 publication. In fact, the '536 publication does not even mention and other long acting paliperidone palmitate than PP1M. It is not the situation where one can just do 3x whatever was done for PP1M to get an idea of what to do for PP3M. While it is true that the same active is present in each, the different nanoparticle sizes make these vastly different formulations that behave differently in the body.

Osborne does nothing to remedy the deficiencies on the '536 publication. Osborne examines data for outcomes of schizophrenic patients when they are long acting injectables versus daily oral medication. It was seen that as patients have to take medications less frequently their schizophrenia is better controlled. This has nothing to do with how to get onto or stay onto the long acting injectables. It also does not discuss what to do if a patient misses a dose of a long acting injectable medication and wishes to get back onto that medication. Osborne merely points out that there may be a benefit of having a patient switch to a long acting injectable medication. The fact that Osborne advises that the best interval for medication administration is 3 months has nothing do to with dealing with missed doses.

Thus, Applicants respectfully request withdrawal of the rejection.

Application Number: 15/090,889  
Docket No.: JPI5001USNP

**Double Patenting Rejection**

Claims 1-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of US 9,439,906 in view of Osborne. Applicants respectfully disagree.

As discussed above, the '906 patent discloses an initiation dosing regimen to get onto PP1M. No such initiation dosing regimen is required for PP3M. The '906 patent does not disclose a dosing regimen for when a dose of PP1M is missed – much less than when a dose of PP3M is missed.

Granting the pending claims in the instant application would not extend the exclusivity that the '906 patent affords the initiation dosing regimen for PP1M as claimed in the '906 patent. The instant claims are solely directed to what patients should do if a dose of PP3M is missed and they desire getting back on the medication. These methods are patentable distinct from how a patient should initially get onto PP1M. Osborne does not remedy the deficiencies of the '906 patent with respect to what to do about missed PP3M doses.

Thus, Applicants respectfully request withdrawal of the rejection.

Application Number: 15/090,889  
Docket No.: JPI5001USNP

**CONCLUSION**

Applicants respectfully submit that the pending claims are in condition for allowance.

Applicants believe that no fee is due for the filing of this submission. However, the Commissioner is hereby authorized to charge any deficiency or credit any overpayments necessitated by this Amendment to Deposit Account No. 10-0750/JAB5001USNP/MW.

Respectfully submitted,

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Dated: February 20, 2018



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 3:20-cv-13103





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## Antipsychotics: How Best to Individualize Treatment

### Quick Case

- BG is a 42-year-old female admitted yesterday for a return of psychosis
- She had been taking an LAI antipsychotic medication dosed once a month
  - She is currently receiving the lowest dose of the injection
  - She has been on the LAI for the past 3 years
  - She missed her last injection that was supposed to be given 2 weeks ago
- What should you do?

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## Examining the Pharmacokinetics and Pharmacodynamics of LAI Antipsychotics: How Best to Individualize Treatment

### What would you do?

- ☐ Restabilize her on oral meds then switch back to LAI
- ☐ Give her an injection of her usual dose plus oral overlap
- ☐ Give her a higher dose of her usual LAI antipsychotic
- ☐ Switch LAI antipsychotics
- ☐ Unsure

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***Janssen Pharmaceuticals, Inc. et al. v. Mylan Laboratories Ltd.***

**U.S. DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY**

**Case No. 20-cv-13103 (EP) (LDW)**

**JANSSEN'S AND MYLAN'S COMBINED DESIGNATIONS OF DEPOSITION TESTIMONY OF  
KATIE REED (FEBRUARY 2, 2022)**

27:12 Q. And what are the timing  
13 considerations that shape the  
14 decision on whether to move forward  
15 with the product?

18 A. So that discussion would  
19 vary. R&D may say that it's going  
20 to take them 12 years to develop  
21 something and we need it, you know,

27:22 within two years. They may say that  
23 in terms of all the other things  
24 that they are working on, you know,  
25 they can't get to it. Or they may

28: 1 REED - CONFIDENTIAL  
2 tell us it's something that they can  
3 get to relatively quickly based on  
4 our previous experience.

32:19 Q. And how do you determine  
20 what that point that Mylan enters  
21 the market will be for your  
22 forecast?

33: 1 REED - CONFIDENTIAL

4 A. The guidance would come  
5 from legal.

6 Q. Is there any other guidance

19 product?

23 A. We don't talk to doctors  
24 and patients. A copy of our FDA  
25 approval labeling will be

204: 1 REED - CONFIDENTIAL

2 distributed with the product when  
3 it's distributed to our customers.

4 Q. So it's the case that Mylan  
5 does not plan to provide any  
6 instructions regarding the use of  
7 its product beyond the FDA approved  
8 label?

9 A. I don't have any knowledge  
10 of anything else being generated  
11 beyond the label.

12 Q. And so Mylan intends for  
13 its product to be used in accordance  
14 with that label?

19 A. Again, we would provide the  
20 label with the product to our  
21 customers and -- I mean they can use  
22 it accordingly, but I would assume  
23 they are going to use it according  
24 to the label that's provided.

211: 3 Q. Other than replacing the  
4 words "Invega Trinza" with the  
5 generic description Paliperidone  
6 Palmitate extended-release  
7 injectable suspension, these missed  
8 dose instructions are identical,

### **CERTIFICATE OF SERVICE**

I hereby certify that I caused a copy of the foregoing document to be filed on March 11, 2024, with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit using the Court's electronic filing system, which will send a notice of electronic filing to all attorneys appearing in this matter.

/s/ Deepro R. Mukerjee